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Design, Synthesis and Preliminary Biological Evaluation of a Focused Combinatorial Library of Stereodiverse Carbohydrate-Scaffold-Based Peptidomimetics

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Abstract—A focused combinatorial library of 126 mimetics of the RGD sequence based on sugar scaffolds have been rationally constructed using molecular modeling, with a particular emphasis on the *stereodiversity* of the library. A liquid phase, mix and divide synthesis was used, active compounds being identified by using orthogonal libraries and recursive deconvolution strategies.

Introduction

Combinatorial chemistry considerably changed the way of finding new molecules and also the way one is thinking chemistry.[1] Most drug research is now concentrated on the finding of lead compounds by high throughput screening of large combinatorial libraries of chemically diverse compounds on a high number of pharmacological targets. As soon as a lead compound is found, a more restricted library is constructed by playing around the original hit compound structure to provide more active compounds. All this process seems to be contradictory to the rational drug design in fast development in the eighties which led, with the help of some knowledge of the biological target and of molecular modeling, to the design and synthesis of only a few candidate molecules.

Between these two approaches, apparently far from each other, there should be a space for an alternative approach, faster than the latter and less costly than the former. It appeared obvious that a rational library design, which may be computer-aided, would lead directly to a focused library able to afford a few lead compounds in a very short time with great chances of success. We tried to make this idea real by studying a defined biological problem: the inhibition of integrin-mediated adhesion, the dysfunction of which is often related to cancer metastasis, angiogenesis and osteoporosis.[2] Among others, the most biologically relevant $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ integrins recognize the short Arg-Gly-Asp (RGD) peptidic sequence exhibited by their proteic ligands, fibronectin, vitronectin and other proteins of the extracellular matrix.[3] A major concern of the adhesion inhibition relies on the selectivity of a protein vis-à-vis of a particular integrin. This selectivity is thought to be related to a bioactive conformation of the RGD sequence which could be specific for its receptor.[4] The design of soluble RGD mimetics has been largely investigated for the inhibition of the fibrinogen-$\alpha_{IIb}\beta_3$ binding mediated platelet aggregation.[5] Only a few selective $\alpha_v\beta_3$ integrin antagonists have been found by screening non-peptide molecules.[6] Some peptide analogues have been proposed[7] and a new class of stereoisomeric peptidic antagonists with high $\alpha_v\beta_3$ selectivity has been reported.[8]

In this work, new selective RGD mimetics based on chiral scaffolds using several original features including computer-aided design of the library and a solution phase combinatorial approach were devised by putting emphasis on stereodiversity.

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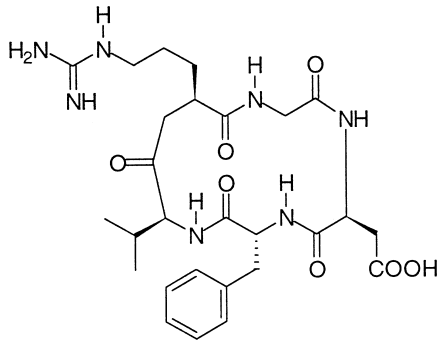
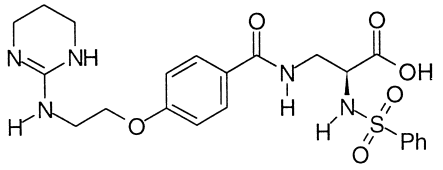
Results

Because the conformation of the RGD sequence of a ligand is believed important in the selective recognition by a given integrin, such conformations were tentatively defined by calculations. This approach proved quite useful in the design[9] and synthesis of some $\alpha_{IIb}\beta_3$ antagonists.[10] Taking advantage of previously reported antagonists of the $\alpha_v\beta_3$ integrin receptor,[8d] a theoretical model of the possible RGD conformations recognized by the $\alpha_v\beta_3$ integrin was built. Furthermore, we decided to construct *stereodiverse* libraries, i.e. containing compounds bearing identical chemical groups but distinct by their respective shapes. To construct such a library, easily accessible scaffolds having different chemical functions suitable for grafting the required amino acid side chain mimics were needed. At first glance, mimicking the RGD sequence can be achieved by using a carboxylic or sulfonic acid residue for aspartic acid and a basic site as a surrogate of the guanidine of the arginine residue, limiting the chemical diversity of the libraries. However, these chemical groups should have different orientations in the space, so that each compound would mimic a given conformation of the native RGD peptidic chain.

Given these requirements, sugar scaffolds seemed excellent candidates owing to the large number of chemical functions, i.e. hydroxyl groups with the different absolute configurations as existing in carbohydrates. Successful uses of sugar scaffolds for peptidomimetics construction can be found in the literature.[10,11] Although combinatorial approaches have been implemented in carbohydrate chemistry,[12,13] to the best of our knowledge, the construction of peptidomimetic libraries on carbohydrate scaffolds is unprecedented.[14]





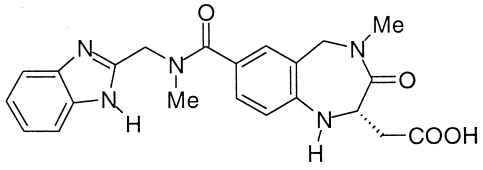


Figure 1. Selective inhibitors of $\alpha_v\beta_3$ integrin.

Theoritical model

These studies began with the construction of a theoretical model of the RGD sequence conformation which should selectively bind to the $\alpha_v\beta_3$ integrin. This would complement our previously described $\alpha_{IIb}\beta_3$ antagonists model.[9] Three highly selective, already existing, antagonists shown in Figure 1 were modeled, of which two arose from peptidomimetics proposed by Merck,[15] SmithKline-Beecham[16] and the third was a rigidified cyclic pentapeptide cyclo-RGDfV proposed by Kessler[4b,8] (Fig. 1). Modeling of these three molecules was performed in two steps.[9b] The first, using simulated annealing, yielded low-energy conformers which were visually compared and gathered in different families. Representative conformations of each of these families were used for subsequent molecular dynamics in a water box to explore the accessible energetic hypersurface. Finally the existing conformers appearing in the course of the dynamics calculations for the three antagonists were superimposed and led to a model of the pharmacophore in which the carboxylic residue had a restricted mobility whereas the basic function, guanidine or a surrogate, had a higher mobility and can occupy a wider space.[17] The resulting model showed an amine–carboxylated distance ranging from 7 to 13 Å (Fig. 2). It is interesting to note that this distance is of the same order of magnitude in the present model and in our already proposed model for $\alpha_{IIb}\beta_3$-selective antagonists.[9] However, it was clear from the latter that these antagonists should need an additional carboxylate or a surrogate. We suggested that these antagonists might mimic the dodecapeptide chain of fibrinogen, the $\alpha_{IIb}\beta_3$-ligand, rather than the RGD sequence.

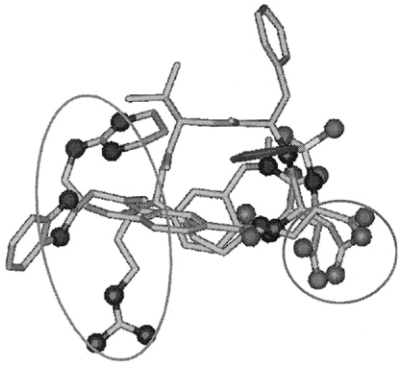


Figure 2. Theoritical model obtained by molecular dynamics: circles represent the possible orientation of the carboxylic acid (right) and the amine groups (left) in the three antagonists in Figure 1.

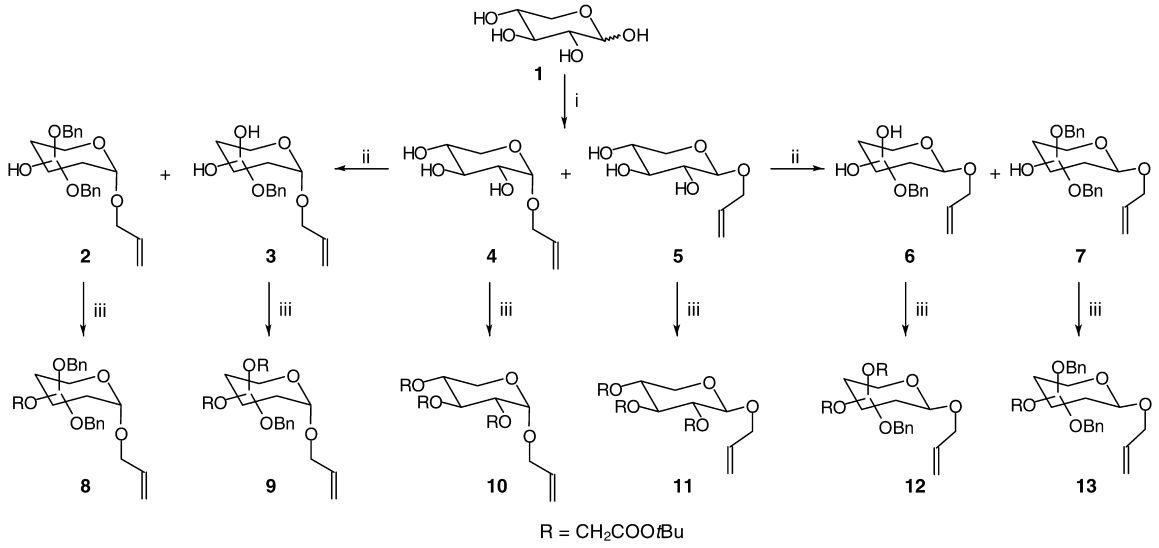
Libraries construction

From theoretical models it was possible to devise new molecules based on a sugar scaffold. The extended

structure of the pharmacophore led to choosing a carbohydrate having all hydroxyl groups equatorially oriented. In addition, the poorly defined bioactive conformation of the arginine side chain led us to probe the surrounding space by using the stereodiversity concept. Thus the use of both anomers would allow a large exploration of the space. One or several carboxylic acid residues should then be introduced on the remaining hydroxyl groups via *O*-alkylation. The use of different anchoring points on the scaffold could modify the amine–carboxylic acid distance, thus allowing the two groups to occupy different spatial arrangements and introducing the stereodiversity. It was then checked by molecular mechanics calculation–geometry optimization that low-energy conformers of some representatives of these structures can more or less adopt conformations in agreement with the theoretical model. At that point a more precise fitting was not required owing to the planned combinatorial approach. Accordingly D-xylose was chosen as an appropriate scaffold having three equatorial hydroxyl groups with the same type of reactivity.[10] A synthetic strategy was then defined which made use of solution phase chemistry and a "mix and divide" strategy to decrease the number of reactions to perform. Thus a deconvolution strategy was needed to allow the identification of the most active compound of the library. In order to ensure that all possible combinations of different stereoisomers would be formed, one and/or two protecting groups, which could also serve as lipophilic groups and could be removed at the end of the synthesis to generate another more hydrophilic library of compounds, were introduced first on allyl D-xyloside.

D-Xylose (**1**) was converted to known allyl D-xylosides under standard conditions.[18] The two anomers were easily separated after acetylation. Subsequent deacetylation afforded the free compounds **4** and **5**, which were separately benzylated using sodium hydride in DMF and different stoichiometries of benzyl bromide. This allowed an almost random benzylation from which extensive chromatographic work allowed us to isolate easily a set of three monobenzylated derivatives **3** and **6** respectively and another set of dibenzylated compounds **2** and **7**. Because the reactivity of the three hydroxyl groups of xylose is not exactly identical, the amount of each isomer in each mixture was not the same. This ratio was corrected in order to work with equal amounts of each product in each mixture. Careful separation of the products yielded pure isomers which were remixed in equal amounts or used to adjust the composition of the original mixture checked by ^{1}H NMR. The six different libraries prepared by this route contained respectively the α-trihydroxy (**4**), α-dihydroxy (**3**), α-monohydroxy derivatives (**2**) and the corresponding β ones (**5**, **6** and **7**).[19] Fourteen different products were prepared this way and used in the following synthetic steps in six different reaction vessels (Scheme 1).

The carboxylic acid residue precursors were introduced by alkylation of the free hydroxyl groups with *tert*-butylbromoacetate to provide the six libraries **8**–**13**. Judicious choice of the components of the libraries, containing only compounds of similar polarity, allowed an easy purification of each library by standard column chromatography. The time was set to prepare the deconvolution steps. The orthogonal design[20] and recursive deconvolution strategies[21] were chosen as a rapid, non-chemical way to identify active compounds. Thus after storage of a portion (30%) of the libraries (**8**–**13**), five new libraries were constructed as follows. All compounds of α configuration were associated in equal amounts in the "α library" **14**. The same was done for the β compounds giving the "β library" **15**. Three new libraries, orthogonal to the two previous ones, were then constructed by mixing compounds containing three (**16**), two (**17**), and one (**18**) ester residues respectively, whatever the anomeric configuration. Thus the fourteen different compounds were split in five different libraries, each compound being present in two different libraries and only two (Fig. 3).



Scheme 1. Reagents: i: (1) Allyl alcohol, Dowex H^+, reflux, (2) Ac_2O, pyridine then separation, (3) MeONa, MeOH; ii: NaH, BnBr, DMF, rt; iii: NaH, $BrCH_2COOtBu$, DMF.

After storage of a portion (30%) of the libraries (**14**–**18**), parallel synthesis was carried out for the introduction of the amine residue. Ozonolysis of the allylic double bond followed by $NaBH_4$ reduction afforded the corresponding alcohols (**19**–**23**). Treatment of the latter with triphenylphosphine and *N*-bromosuccinimide gave the corresponding bromides (**24**–**28**) in good to excellent yield (Scheme 2). Monitoring of these reactions was easily performed by ^{13}C NMR. A portion of the five mixtures of bromides was set aside and the new library **29** of fourteen different bromo derivatives was prepared by mixing the five preceding mixtures in equal amounts. This final mixture **29** of fourteen bromides was split into nine different reaction vessels and treated in parallel with nine different primary amines in an S_N2 reaction followed by BOC protection of the resulting secondary amine to facilitate purification. This provided a library of 126 compounds split into nine mixtures **30a–i**. The different amino groups, which brought chemical diversity to the library, were selected from literature precedents (Fig. 4). Finally libraries **30a–i** were treated with trifluoroacetic acid to remove all protecting groups giving nine different mixtures **31a–i**.

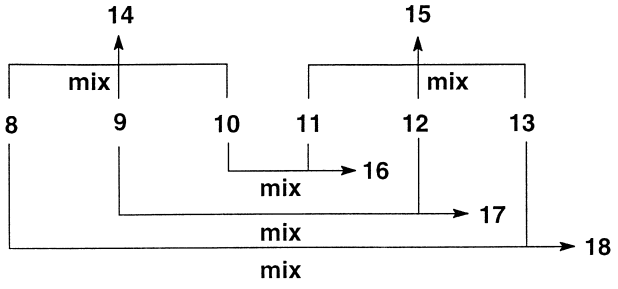
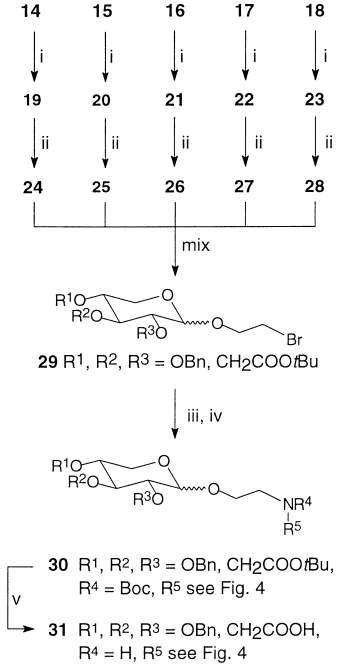


Figure 3. Construction of the orthogonal libraries **14**, **15/16**–**18** by mixing sub-libraries **8**–**13**.

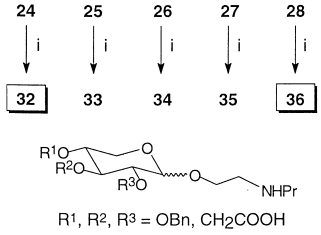


Scheme 2. Reagents: i: (1) O_3, MeOH/THF, −70 °C; (2) $NaBH_4$; ii: PPh_3, NBS, DMF, 50 °C; iii: R^5NH_2, DMF, 70 °C; iv: BOC_2O, NEt_3, CH_2Cl_2; v: TFA:H_2O, 3:1.

Preliminary biological testings and deconvolution

The biological evaluation of these nine mixtures was carried out by estimating the adhesion of S180 sarcoma cells, which express only $\alpha_v\beta_3$ integrin, on a substrate of fibronectin or vitronectin in the presence of the compounds and compared to the effect of the RGDS peptide as reference on the same cells. Mixtures **31a**,**b**,**d** and **i** showed significant adhesion inhibitory activities (Fig. 5). In particular compounds having an *N*-propyl substituent contained in library **31a** were active and were thus further investigated to identify the most active compound among the fourteen different possible products.

The previously stored five mixtures **24**–**28** of brominated derivatives were treated individually with propylamine to provide the corresponding five orthogonal sub-libraries of compounds **32**–**36**. (Scheme 3) These five mixtures were tested as above and, among others, two sub-libraries **32** containing α compounds and **36** containing dibenzylated derivatives were found active (Fig. 6). Obviously the active molecule should be of α configuration and should have two benzyl groups. Only three compounds have these characteristics (Fig. 7). Normally the synthesis of the three pure compounds would give the expected most active structure. In order



Scheme 3. Reagents: i: (1) $PrNH_2$, DMF, 70 °C, 2 h; (2) BOC_2O, NEt_3, CH_2Cl_2; (3) TFA:H_2O, 3:1.

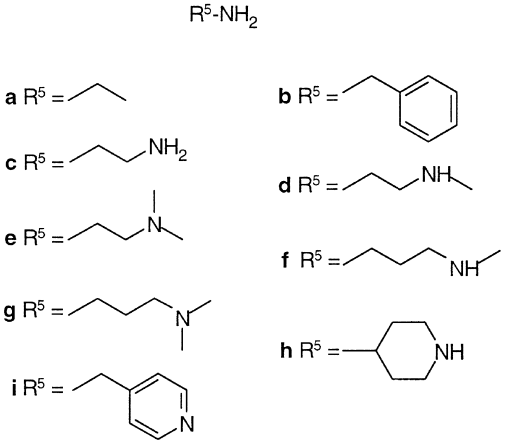


Figure 4. Structures of the different amines used for libraries construction.

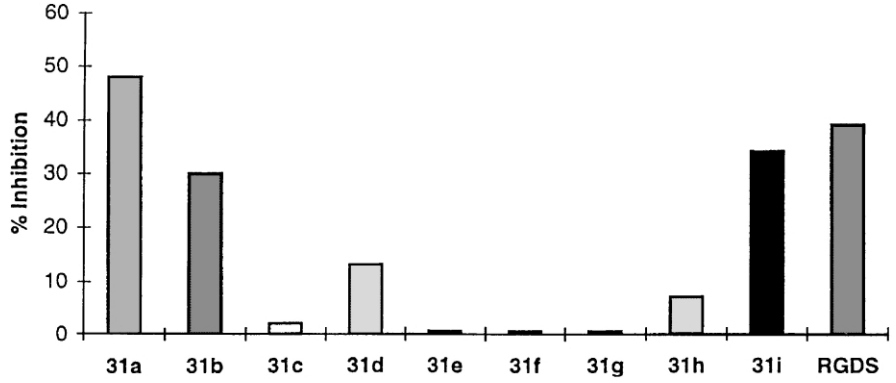


Figure 5. Inhibition of cell adhesion on vitronectin substratum at 1 mg/mL of libraries **31a–i**.

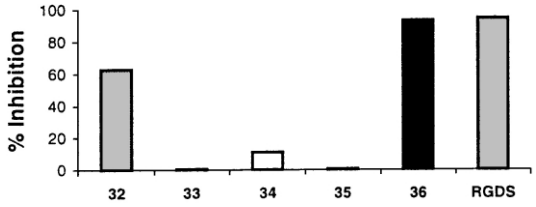
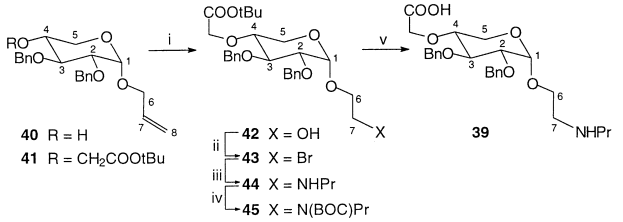


Figure 6. Inhibition of cell adhesion on vitronectin substratum at 2 mg/mL of orthogonal libraries **32**–**36**.



Scheme 4. Reagents and conditions: i: (1) O_3, MeOH/THF-70 °C; (2) $NaBH_4$; ii: PPh_3, NBS, DMF 50 °C; iii: $C_3H_7NH_2$, DMF, 70 °C; iv: BOC_2O, NEt_3, CH_2Cl_2; v: TFA:H_2O, 3:1.

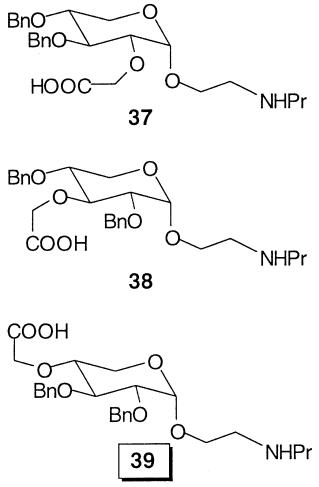


Figure 7. Final active mixture (**39** was the active compound).

to shorten the deconvolution process we decided to turn back to the theoretical model of the RGD sequence and we checked which of the three compounds **37**, **38** and **39** would have a chance to adopt a conformation fitting with the model. Molecular dynamics calculations clearly showed that the compound **39** having the carboxylic acid grafted at position 4 was the best candidate. Its synthesis was then carried out from the corresponding allyl 2,3-di-*O*-benzyl-α-D-xyloside (**40**) in 6 steps in an overall yield of 76% (Scheme 4). The biological activity of this compound in this test was identical to that of RGDS, both compounds being tested at a 2 mg/mL concentration (ca. 4 mM).

In conclusion we have presented one of the first example of carbohydrate-based libraries of peptidomimetics using the stereodiversity concept. This stereodiversity, provided by the use of a single judiciously substituted carbohydrate scaffold, is an important feature of our library and it represents an excellent way to mimic different conformations of the same peptide chain. Only one carbohydrate scaffold was used in this study, the stereodiversity being simply introduced by playing with the different hydroxyl groups. It is clear that the use of different carbohydrate scaffolds would increase the possibilities of our approach. A new dimension should be introduced in combinatorial chemistry by emphasizing stereochemical and regiochemical diversity rather than chemical diversity. Some compounds with modest activities as antagonists of $\alpha_v\beta_3$ integrin have been identified. Further biological testings of the libraries are underway. Having established the validity of this approach we are currently applying this concept to the construction of other biologically relevant libraries of peptidomimetics and in the design of synthetic receptors using parallel synthesis.

Experimental

General indications

All reactions were performed under nitrogen atmosphere. Melting points are uncorrected and recorded with a Büchi capillary tube melting-point apparatus. Optical rotations were measured on a Perkin Elmer 141

polarimeter in a 1 dm cell at 20 °C. FTIR spectra were recorded on Perkin Elmer Spectrum 1000 on NaCl windows or KBr pellets. ^{1}H (250 MHz) and ^{13}C NMR (62.5 MHz) spectra were recorded on a Bruker AC 250 spectrometer. Unless otherwise stated, all spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm using the residual of chloroform as internal standard (7.27 ppm and 77.0 ppm respectively). Attribution of ^{13}C signals are based on the *J*-modulated spin-echo sequence. Mass spectra were recorded on a Trio 1000 Thermo Quest spectrometer in the electron impact mode or a Platform Micromass in the electrospray mode. Elemental analyses were obtained from the Service Central de Microanalyse du CNRS, Vernaison (France). Analytical thin-layer chromatography was performed on Merck $60F_{254}$ pre-coated silica gel plates. Preparative chromatography was performed on silica gel 60 (230-40 mesh ASTM) using ethyl acetate (E) and hexane (H) mixtures.

Computational details. All calculations were performed with the Insight 97.0/Discover package using the CVFF force field on Silicon Graphics® Indigo2 workstations. Molecular dynamics simulations were carried out using a time step of 1 fs. Optimizations were performed by conjugate gradient energy minimization with a convergence criterion of 0.001 kcal/mol. Atom partial charges were calculated using MNDO semiempirical method by calculation of the Mulliken electronic population. For in vacuo simulations, solvent conditions were represented implicitly using a distance-dependent dielectric constant $\epsilon = r$. For dynamics simulations with explicit water molecules, periodic boundary conditions were applied, using water model provided by MSI and a fixed dielectric constant of 1.0. Conformational samplings and molecular dynamics in explicit solvent were performed according to the previously reported procedures.[9b]

Cell cultures and reagents. The sarcoma 180 cells used in this study were a sub-clone derived by Dr. K. Yamada (NIH, Bethesda, USA) from the original parental cell line, which was obtained from ATCC (CCL8; CCRF S180 II). These cells were selected for their inability to assemble a fibronectin (FN) matrix at the cell surface. They were cultured in Dubelcco's modified Eagle's medium (DMEM) containing 10% (v/v) fetal calf serum (FCS), penicillin (100 I.U./mL)–streptomycin (100 μg/mL) and 2 mM L-glutamine (Seromed) in a 37 °C incubator under an atmosphere of 6% CO_2/94% air. Fibronectin, vitronectin and RGDS peptides were purchased from Sigma.

Libraries construction: chemistry

Non selective benzylation. NaH (1.11 g, 27.7 mmol) was suspended in DMF (80 mL) and allyl D-xyloside (5.25 g, 27.7 mmol) in DMF (100 mL) was added dropwise at 0 °C. After stirring for 30 min, benzyl bromide (3.3 mL, 27.7 mmol) was added in one portion at room temperature. The resulting mixture was stirred for 16 h then quenched with methanol (10 mL) at 0 °C. The solution was concentrated in vacuo then taken up in dichloromethane, washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (H:E, 4:1 then 1:1 then 2:3) to provide the monobenzylated derivatives (3.93 g, 13.6 mmol, 49%), and the three dibenzylated compounds (1.1 g, 3 mmol, 11%) as well as some of the tribenzylated derivative (0.25 g, 0.6 mmol, 2%).

Each pure component of mixture **2** was prepared and characterized.

Allyl 2,3-di-*O*-benzyl-α-D-xylopyranoside. $R_f = 0.19$ (H:E, 4:1); $[\alpha]_D$ +44.7 (*c* 1.0, $CHCl_3$); IR: 3436 cm^{-1}; ^{1}H NMR: δ 2.52 (s, 1H, O*H*), 3.52 (dd, 1H, $J_{4,5}$ 4, $J_{5,5'}$ 9 Hz, *H*-5), 3.63 (m, 2H, *H*-2, *H*-3), 3.77 (ddd, 1H, $J_{3,4}$ 8.5, $J_{4,5'}$ 9 Hz, *H*-4), 4.01 (ddd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6, $J_{6,8}$ 1 Hz, *H*-6), 4.04 (dd, 1H, *H*-5′), 4.23 (ddd, 1H, $J_{66',7}$ 5 Hz, $J_{6',8}$ 1 Hz, *H*-6′), 4.68 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.71 (s, 2H, CH_2Ph), 4.78 (d, 1H, $J_{1,2}$ 4 Hz, *H*-1), 4.96 (d, 1H, CH_2Ph), 5.24 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.33 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.95 (m, 1H, *H*-7), 7.35 (m, 10H, Ph); ^{13}C NMR: δ 61.9 (1C, *C*-5), 68.0 (1C, *C*-6), 69.3 (1C, *C*-4), 72.8, 74.7 (2C, *C*H$_2$Ph), 79.0 (1C, *C*-2), 80.9 (1C, *C*-3), 95.7 (1C, *C*-1), 117.7 (1C, *C*-8), 127.6, 127.7, 128.1 (10C, *C*H Ph), 133.6 (1C, *C*-7), 137.8, 138.5 (2C, *C* Ph). Anal. calcd for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1. Found: C, 71.71; H, 7.21.

Allyl 2,4-di-*O*-benzyl-α-D-xylopyranoside. $R_f = 0.28$ (H:E, 4:1); $[\alpha]_D$ +72.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR: δ 2.58 (d, 1H, $J_{H,OH}$ 2 Hz, O*H*), 3.34 (dd, 1H, $J_{4,5}$ 4, $J_{5,5'}$ 9 Hz, *H*-5), 3.53 (m, 3H, *H*-2, *H*-3, *H*-4), 3.92 (ddd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6, $J_{6,8}$ 1 Hz, *H*-6), 4.04 (dd, 1H, $J_{4,5'}$ 9 Hz, *H*-5′), 4.13 (ddd, 1H, $J_{6',7}$ 5, $J_{6',8}$ 1 Hz, *H*-6′), 4.64 (2d, 2H, J_{gem} 12 Hz, CH_2Ph), 4.67 (d, 1H, $J_{1,2}$ 4 Hz, *H*-1), 4.76 (d, 1H, CH_2Ph), 4.78 (d, 1H, CH_2Ph), 5.21 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.32 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.90 (m, 1H, *H*-7), 7.33 (m, 10H, Ph); ^{13}C NMR: δ 59.3 (1C, *C*-5), 67.7 (1C, *C*-6), 72.2 (1C, *C*-3), 72.4, 72.7 (2C, *C*H$_2$Ph), 77.2 (1C, *C*-4), 79.0 (1C, *C*-2), 95.0 (1C, *C*-1), 117.7 (1C, *C*-8), 127.31, 127.35, 127.43, 127.57, 127.93, 127.97, 128.00 (10C, *C*H Ph), 133.4 (1C, *C*-7), 137.7, 138.0 (2C, *C* Ph).

Allyl 3,4-di-*O*-benzyl-α-D-xylopyranoside. $R_f = 0.26$ (H:E, 4:1); $[\alpha]_D$ +90.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 2.29 (d, 1H, $J_{H,OH}$ 8 Hz, O*H*), 3.55 (bm, 3H, *H*-3, *H*-4, *H*-5), 3.69 (bm, 1H, *H*-2), 4.02 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6, *H*-6), 4.04 (dd, 1H, $J_{4,5'}$ 9 Hz, *H*-5′), 4.22 (dddd, 1H, $J_{6',7}$ 5, $J_{6',8}$ 1, $J_{6',8'}$ 1 Hz, *H*-6′), 4.63 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.73 (d, 1H, CH_2Ph), 4.85 (d, 1H, $J_{1,2}$ 4 Hz, *H*-1), 4.85 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.91 (d, 1H, CH_2Ph), 5.21 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.31 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.92 (m, 1H, *H*-7), 7.33 (m, 10H, Ph); ^{13}C NMR: δ 60.1 (1C, *C*-5), 68.1 (1C, *C*-6), 72.0 (1C, *C*-2), 72.9, 74.8 (2C, *C*H$_2$Ph), 77.3 (1C, *C*-4), 81.6 (1C, *C*-3), 97.3 (1C, *C*-1), 117.5 (1C, *C*-8), 127.3, 127.5, 127.53, 127.58, 128.08, 128.16 (10C, *C*H Ph), 133.5 (1C, *C*-7), 137.9, 138.5 (2C, *C* Ph).

Mixture 3

Allyl 2-*O*-benzyl-α-D-xylopyranoside. $R_f = 0.60$ (H:E, 1:4); $[\alpha]_D$ +107.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ 2.59 (bs, 1H, O*H*), 2.72 (bs, 1H, O*H*), 3.32 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$

10 Hz, *H*-2), 3.54 (m, 3H, *H*-4, *H*-5, *H*-5′), 3.87 (dd, 1H, $J_{3,4}$ 5 Hz, *H*-3), 3.91 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6 Hz, *H*-6), 4.15 (dd, 1H, $J_{6',7}$ 5 Hz, *H*-6′), 4.60 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.68 (d, 1H, C*H*$_2$Ph), 4.76 (d, 1H, *H*-1), 5.21 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.32 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.89 (m, 1H, *H*-7), 7.33 (m, 5H, Ph); ^{13}C NMR: δ 61.3 (1C, *C*-5), 67.8 (1C, *C*-6), 69.8 (1C, *C*-4), 72.6 (1C, *C*H$_2$Ph), 72.9 (1C, *C*-2), 79.1 (1C, *C*-3), 95.4 (1C, *C*-1), 116.8 (1C, *C*-8), 127.6, 127.8, 128.1 (5C, *C*H Ph), 133.6 (1C, *C*-7), 137.9 (1C, *C* Ph). EIMS: *m*/*z*: 280.7 $(M)^{+\bullet}$, 91 (Bn). Anal. calcd for $C_{15}H_{20}O_5$: C, 64.3; H, 7.2. Found: C, 64.06%; H, 7.13%.

Allyl 3-*O*-benzyl-α-D-xylopyranoside. R_f = 0.63 (H:E, 1:4); mp 92 °C (CH_2Cl_2/H); $[\alpha]_D$ +68.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ 2.29 (d, 1H, $J_{H,OH}$ 7.5 Hz, O*H*), 2.56 (s, 1H, O*H*), 3.66 (m, 5H, *H*-2, *H*-3, *H*-4, *H*-5, *H*-5′), 4.04 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6.5 Hz, *H*-6), 4.30 (dd, 1H, $J_{6',7}$ 5.5 Hz, *H*-6′), 4.70 (d, 1H, J_{gem} 11.5 Hz, C*H*$_2$Ph), 4.80 (d, 1H, $J_{1,2}$ 3 Hz, *H*-1), 4.94 (d, 1H, C*H*$_2$Ph), 5.23 (dd, 1H, $J_{7,8}$ 10.5 Hz, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.32 (dd, 1H, $J_{7,8'}$ 15.5 Hz, *H*-8′), 5.92 (m, 1H, *H*-7), 7.35 (m, 5H, Ph); ^{13}C NMR: δ 62.7 (1C, *C*-5), 68.5 (1C, *C*-6), 68.7 (1C, *C*-4), 71.8 (1C, *C*-2), 74.2 (1C, *C*H$_2$Ph), 81.6 (1C, *C*-3), 97.5 (1C, *C*-1), 117.8 (1C, *C*-8), 127.7, 128.4 (5C, *C*H Ph), 133.5 (1C, *C*-7), 138.2 (1C, *C* Ph). Anal. calcd for $C_{15}H_{20}O_5$: C, 64.3; H, 7.2. Found: C, 64.40; H, 7.04.

Allyl 4-*O*-benzyl-α-D-xylopyranoside. R_f = 0.60 (H:E, 1:4); ^{1}H NMR: δ 2.23 (d, 1H, $J_{H,OH}$ 7 Hz, O*H*), 2.78 (bs, 1H, O*H*), 3.50 (m, 3H, *H*-2, *H*-5, *H*-5′), 3.68 (m, 1H, *H*-4), 3.82 (dd, 1H, $J_{2,3} = J_{3,4}$ 8 Hz, *H*-3), 3.99 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6 Hz, *H*-6), 4.21 (dd, 1H, $J_{6',7}$ 5 Hz, *H*-6′), 4.64 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.72 (d, 1H, C*H*$_2$Ph), 4.84 (d, 1H, $J_{1,2}$ 4.5 Hz, *H*-1), 5.21 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.28 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.91 (m, 1H, *H*-7), 7.33 (m, 5H, Ph); ^{13}C NMR: δ 59.6 (1C, *C*-5), 67.7 (1C, *C*-6), 71.7 (1C, *C*-2), 72.6 (1C, *C*H$_2$Ph), 73.1 (1C, *C*-3), 77.2 (1C, *C*-4), 97.0 (1C, *C*-1), 117.0 (1C, *C*-8), 127.2, 127.3, 127.8 (5C, *C*H Ph), 133.5 (1C, *C*-7), 138.0 (1C, *C* Ph).

Mixture 6

Allyl 2-*O*-benzyl-β-D-xylopyranoside. R_f = 0.33 (H:E, 2:3); mp 64 °C (CH_2Cl_2/H); $[\alpha]_D$ −11.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR: δ 3.09 (bs, 2H, O*H*), 3.37 (dd, 1H, $J_{4,5}$ 9.5, $J_{5,5'}$ 11.5 Hz, *H*-5), 3.40 (dd, 1H, $J_{1,2}$ 7.5, $J_{2,3}$ 5.5 Hz, *H*-2), 3.64 (m, 2H, *H*-3, *H*-4), 4.01 (dd, 1H, $J_{4,5'}$ 3.5 Hz, *H*-5′), 4.08 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6.5 Hz, *H*-6), 4.33 (dddd, 1H, $J_{6',7}$ 5, $J_{6',8}$ 1, $J_{6',8'}$ 1 Hz, *H*-6′), 4.61 (d, 1H, *H*-1), 4.65 (d, 1H, J_{gem} 11.5 Hz, C*H*$_2$Ph), 4.84 (d, 1H, C*H*$_2$Ph), 5.22 (ddd, 1H, $J_{7,8}$ 11, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.31 (ddd, 1H, $J_{7,8'}$ 17.5 Hz, *H*-8′), 5.92 (m, 1H, *H*-7), 7.33 (m, 5H, Ph); ^{13}C NMR: δ 64.7 (1C, *C*-5), 69.2 (1C, *C*-4), 69.4 (1C, *C*-6), 73.8 (1C, *C*H$_2$Ph), 75.0 (1C, *C*-3), 80.3 (1C, *C*-2), 102.2 (1C, *C*-1), 116.9 (1C, *C*-8), 127.3, 127.6, 127.8 (5C, *C*H Ph), 133.5 (1C, *C*-7), 138.0 (1C, *C* Ph). Anal. calcd for $C_{15}H_{20}O_5$: C, 64.3; H, 7.2. Found: C, 64.16; H, 7.12.

Allyl 3-*O*-benzyl-β-D-xylopyranoside. R_f = 0.63 (H:E, 1:1); mp 96 °C (CH_2Cl_2/H); $[\alpha]_D$ −56.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR: δ 2.20 (d, 1H, $J_{H,OH}$ 3 Hz, O*H*), 2.43 (d, 1H, $J_{H,OH}$ 2.5 Hz, O*H*), 3.26 (dd, 1H, $J_{4,5}$ 9.5, $J_{5,5'}$ 12 Hz, *H*-5), 3.38 (dd, 1H, $J_{2,3} = J_{3,4}$ 8 Hz, *H*-3), 3.57 (ddd, 1H, $J_{1,2}$ 8 Hz, *H*-2), 3.73 (ddd, 1H, $J_{4,5'}$ 5 Hz, *H*-4), 4.02 (dd, 1H, *H*-5′), 4.12 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6 Hz, *H*-6), 4.31 (d, 1H, *H*-1), 4.36 (dd, 1H, $J_{6',7}$ 5 Hz, *H*-6′), 4.74 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 5.00 (d, 1H, C*H*$_2$Ph), 5.23 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.33 (dd, 1H, $J_{7,8'}$ 16.5 Hz, *H*-8′), 5.94 (m, 1H, *H*-7), 7.34 (m, 5H, Ph); ^{13}C NMR: δ 65.0 (1C, *C*-5), 69.2 (1C, *C*-4), 70.1 (1C, *C*-6), 73.4 (1C, *C*-2), 74.4 (1C, *C*H$_2$Ph), 83.10 (1C, *C*-3), 102.30 (1C, *C*-1), 118.03 (1C, *C*-8), 127.9, 128.1, 128.6 (5C, *C*H Ph), 133.9 (1C, *C*-7), 138.6 (1C, *C* Ph).

Allyl 4-*O*-benzyl-β-D-xylopyranoside. R_f = 0.38 (H:E, 2:3); $[\alpha]_D$ −77.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 3.14 (d, 1H, $J_{H,OH}$ 6.5 Hz, O*H*), 3.21 (d, 1H, $J_{H,OH}$ 7 Hz, O*H*), 3.50 (m, 1H, *H*-4), 3.55 (m, 2H, *H*-2, *H*-5), 3.82 (ddd, 1H, $J_{2,3} = J_{3,4}$ 8 Hz, *H*-3), 4.02 (dd, 1H, $J_{4,5'}$ 5, $J_{5,5'}$ 12 Hz, *H*-5′), 4.08 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6 Hz, *H*-6), 4.30 (dd, 1H, $J_{6',7}$ 5.5 Hz, *H*-6′), 4.60 (d, 1H, $J_{1,2}$ 4.5 Hz, *H*-1), 4.68 (s, 2H, C*H*$_2$Ph), 5.23 (dd, 1H, $J_{7,8}$ 11, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.30 (dd, 1H, $J_{7,8'}$ 17.5 Hz, *H*-8′), 5.92 (m, 1H, *H*-7), 7.35 (m, 5H, Ph); ^{13}C NMR: δ 62.3 (1C, *C*-5), 69.5 (1C, *C*-6), 71.5 (1C, *C*H$_2$Ph), 72.3 (1C, *C*-2), 73.7 (1C, *C*-3), 76.7 (1C, *C*-4), 101.4 (1C, *C*-1), 117.6 (1C, *C*-8), 127.5, 127.6, 128.0 (5C, *C*H Ph), 133.5 (1C, *C*-7), 137.7 (1C, *C* Ph).

Mixture 7

Allyl 2,3-di-*O*-benzyl-β-D-xylopyranoside. R_f = 0.29 (H:E, 4:1); mp 67 °C (CH_2Cl_2/H); $[\alpha]_D$ −32.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR: δ 2.31 (d, 1H, $J_{H,OH}$ 4.5 Hz, O*H*), 3.26 (dd, 1H, $J_{4,5}$ 8.5, $J_{5,5'}$ 11.5 Hz, *H*-5), 3.45 (dd, 1H, $J_{2,3}$ 5, $J_{3,4}$ 5 Hz, *H*-3), 3.67 (m, 1H, *H*-4), 4.01 (dd, 1H, $J_{4,5'}$ 5 Hz, *H*-5′), 4.11 (ddd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6, $J_{6,8}$ 0.5 Hz, *H*-6), 4.37 (ddd, 1H, $J_{6',7}$ 6, $J_{6',8}$ 0.5 Hz, *H*-6′), 4.50 (dd, $J_{1,2}$ 5 Hz, *H*-2), 4.61 (d, 1H, *H*-1), 4.63 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.68 (d, 1H, C*H*$_2$Ph), 4.90 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.91 (d, 1H, C*H*$_2$Ph), 5.21 (ddd, 1H, $J_{7,8}$ 10, $J_{8,8'}$ 0.5 Hz, *H*-8), 5.30 (dd, 1H, $J_{7,8'}$ 18 Hz, *H*-8′), 5.92 (m, 1H, *H*-7), 7.33 (m, 10H, Ph); ^{13}C NMR: δ 64.5 (1C, *C*-5), 69.1 (1C, *C*-4), 69.7 (1C, *C*-6), 74.1, 74.4 (2C, CH_2Ph), 80.4 (1C, *C*-2), 82.5 (1C, *C*-3), 102.3 (1C, *C*-1), 117.1 (1C, *C*-8), 127.54, 127.57, 127.65, 127.71, 127.90, 128.18, 128.27 (10C, *C*H Ph), 133.7 (1C, *C*-7), 138.0, 138.3 (2C, *C* Ph). Anal. calcd for $C_{23}H_{28}O_4$: C, 71.3; H, 7.1. Found: C, 71.16; H, 7.23.

Allyl 2,4-di-*O*-benzyl-β-D-xylopyranoside. R_f = 0.40 (H:E, 4:1); $[\alpha]_D$ +1.8 (*c* 1.6, $CHCl_3$); ^{1}H NMR: δ 2.53 (d, 1H, $J_{H,OH}$ 2.5 Hz, O*H*), 3.22 (dd, 1H, $J_{4,5}$ 10, $J_{5,5'}$ 12 Hz, *H*-5), 3.27 (dd, 1H, $J_{1,2}$ 7.5, $J_{2,3}$ 9 Hz, *H*-2), 3.51 (ddd, 1H, $J_{3,4}$ 9, $J_{4,5'}$ 5 Hz, *H*-4), 3.68 (m, 1H, *H*-3), 3.93 (dd, 1H, *H*-5′), 4.11 (ddd, 1H, $J_{6,6'}$ 12.5, $J_{6,7}$ 6, $J_{6,8}$ 0.5 Hz, *H*-6), 4.37 (ddd, 1H, $J_{6',7}$ 5, $J_{6',8}$ 0.5 Hz, *H*-6′), 4.40 (d, 1H, *H*-1), 4.62 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.68 (d, 1H, C*H*$_2$Ph), 4.76 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.94 (d, 1H, C*H*$_2$Ph), 5.22 (ddd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 0.5 Hz, *H*-8), 5.33 (dd, 1H, $J_{7,8'}$ 17.5 Hz, *H*-8′), 5.94 (m, 1H, *H*-7), 7.34 (m, 10H, Ph); ^{13}C NMR: δ 63.5 (1C, *C*-5), 69.7 (1C, *C*-6), 72.7, 74.1 (2C, *C*H$_2$Ph), 75.2 (1C, *C*-3), 76.9 (1C, *C*-4), 80.8 (1C, *C*-2), 102.5 (1C, *C*-1), 117.0 (1C, *C*-8), 127.44,

127.51, 127.75, 128.12, 128.15 (10C, *C*H Ph), 133.7 (1C, *C*-7), 138.0, 138.2 (2C, *C* Ph).

Allyl 3,4-di-*O*-benzyl-β-D-xylopyranoside. $R_f = 0.32$ (H:E, 4:1); $[\alpha]_D$ −11.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR: δ 2.63 (d, 1H, $J_{H,OH}$ 2.5 Hz, O*H*), 3.32 (dd, 1H, $J_{4,5}$ 8, $J_{5,5'}$ 12 Hz, *H*-5), 3.59 (m, 3H, *H*-2, *H*-3, *H*-4), 4.02 (dd, 1H, $J_{4,5'}$ 4.5 Hz, *H*-5′), 4.12 (dd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 6.5 Hz, *H*-6), 4.35 (dd, 1H, $J_{6',7}$ 5 Hz, *H*-6′), 4.40 (d, 1H, $J_{1,2}$ 6 Hz, *H*-1), 4.64 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.72 (d, 1H, CH_2Ph), 4.86 (s, 2H, CH_2Ph), 5.23 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1 Hz, *H*-8), 5.33 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.96 (m, 1H, *H*-7), 7.34 (m, 10H, Ph); ^{13}C NMR: δ 64.6 (1C, *C*-5), 67.9 (1C, *C*-6), 72.5 (1C, *C*-2), 72.9, 74.2 (2C, *C*H_2Ph), 76.7 (1C, *C*-4), 81.6 (1C, *C*-3), 101.7 (1C, *C*-1), 117.4 (1C, *C*-8), 127.36, 127.54, 127.61, 127.73, 127.88, 128.08, 128.17 (10C, *C*H Ph), 133.7 (1C, *C*-7), 137.7, 138.3 (2C, *C* Ph).

Typical procedures

The following procedures have been used for the preparation of libraries **31**.

Alkylation. NaH (849 mg, 21.2 mmol) was suspended in DMF (50 mL) and allyl β-D-xyloside (1.00 g, 5.26 mmol) in DMF (50 mL) was added dropwise at 0 °C. To this suspension was subsequently added *tert*-butylbromoacetate (5 mL). The resulting mixture was stirred for 16 h then quenched with methanol (5 mL) at 0 °C. The solution was concentrated in vacuo then taken up in dichloromethane, washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (H:E, 9:1 then 4:1) to provide **11** (2.15 mg, 4.04 mmol, 77%).

Ozonolysis. O_3 was bubbled through a vigorously stirred solution of the olefin (1 mmol) in a mixture of MeOH: THF (20 mL, 2:1) at −78 °C until starting material disappearance (TLC monitoring) then sodium borohydride (168 mg, 1.06 mmol) was added. Purification by chromatography (H:E, 4:1 then 3:2) afforded the alcohol (90–96%).

Bromination. To a solution of the alcohol (1.0 mmol) and *N*-bromosuccinimide (354 mg, 2 mmol) in DMF was added triphenylphosphine (524 mg, 2 mmol). The mixture was warmed up to 70 °C and stirred for a further 30 min. The reagent in excess was quenched with methanol (2 mL) and the mixture was concentrated *in* vacuo. The residue was chromatographed (H:E, 4:1) to yield the bromo derivative (70–76%).

Amination/protection. The bromo-derivative (1 mmol) was refluxed in DMF (20 mL) in the presence of amine (5 mL) for 30 min. After concentration in vacuo, the crude product was treated by BOC_2O (0.25 mL) and triethylamine (0.14 mL) in dichloromethane (10 mL) for 1 h to afford the pure BOC protected derivative after column chromatography (85–92%).

Deprotection. The protected compound was stirred in a TFA:water mixture (3:1) for 16 h. The concentration in vacuo, followed by dilution in water and lyophilization led to the trifluoroacetate salts as foams (80–90%).

Libraries characterization

All mixtures were characterized by ^{13}C NMR. Obviously, due to signal overlap, the number of peaks assigned to a group of identical carbon atoms can differ from the expected one. (See Scheme 4 for carbon numbering.)

Mixture 8 (3 compounds). 92%; $R_f = 0.55$–0.70 (H:E, 4:1); ^{13}C NMR: δ 27.47, 27.53, 27.60 (3×3C, O*t*Bu), 59.53, 59.63, 59.64 (3×1C, *C*-5), 67.51, 67.70, 67.88 (3×1C, *C*-6), 69.04, 69.25, 70.79, 72.57, 72.73, 72.78, 72.94, 75.12 (3×3C, *C*H_2Ph, *C*H_2COO*t*Bu), 77.15, 77.95, 78.70, 78.99, 79.36, 80.11, 81.22, 81.31, 82.20 (3×3C, *C*-2, *C*-3, *C*-4), 80.43, 80.85, 81.06 (3×1C, O*t*Bu), 95.09, 95.26, 96.38 (3×1C, *C*-1), 116.98, 117.23, 117.37 (3×1C, *C*-7), 127.09, 127.13, 127.19, 127.29, 127.47, 127.56, 127.85, 127.89 (3×10C, *C*H Ph), 133.38, 133.42, 133.57 (3×1C, *C*-8), 137.82, 137.86, 137.98, 138.35, 138.45 (3×2C, *C* Ph), 168.86, 168.91, 169.21 (3×1C, *C*OO*t*Bu).

Mixture 9 (3 compounds). 84%; $R_f = 0.55$–0.70 (H:E, 4:1); ^{13}C NMR: δ 27.54, 27.59, 27.66 (3×6C, O*t*Bu), 59.39, 59.55, 59.63 (3×1C, *C*-5), 67.56, 67.74, 67.78 (3×1C, *C*-6), 68.96, 69.10, 69.18, 69.22, 70.69, 70.80, 72.62, 73.60, 75.16 (3×3C, *C*H_2Ph, *C*H_2COO*t*Bu), 77.74, 77.96, 79.11, 79.27, 79.42, 80.22, 81.58, 82.58, 82.76 (3×3C, *C*-2, *C*-3, *C*-4), 80.58, 80.68, 80.84, 80.97, 81.06, 81.13 (3×2C, O*t*Bu), 95.06, 95.24, 96.34 (3×1C, *C*-1), 117.04, 117.12, 117.40 (3×1C, *C*-7), 127.27, 127.34, 127.37, 127.54, 127.78, 127.98 (3×5C, *C*HPh), 133.37, 133.54, 133.57 (3×1C, *C*-8), 137.84, 137.92, 138.25 (3×1C, *C* Ph), 168.52, 168.88, 168.99, 169.03, 169.26, 169.50 (3×2C, *C*OO*t*Bu).

Compound 10. 77%; $R_f = 0.55$ (H:E, 4:1); ^{13}C NMR: δ 28.01, 28.34 (9C, O*t*Bu), 59.74 (1C, *C*-5), 68.14 (1C, *C*-6), 69.26, 69.39, 71.03 (3C, *C*H_2COO*t*Bu), 78.99 (1C, *C*-4), 79.99 (1C, *C*-2), 81.17, 81.42, 81.49 (3C, O*t*Bu), 83.21 (1C, *C*-3), 96.36 (1C, *C*-1), 117.64 (1C, *C*-7), 133.71 (1C, *C*-8), 169.31, 169.64, 169.71 (3C, *C*OO*t*Bu).

Compound 11. 77%; $R_f = 0.59$ (H:E, 4:1); ^{13}C NMR: δ 27.93, 27.96 (9C, O*t*Bu), 63.8 (1C, *C*-5), 69.3 (1C, *C*-6), 69.8, 70.8 (3C, *C*H_2COO*t*Bu), 77.5 (1C, *C*-4), 80.8, 80.9, 81.1 (3C, O*t*Bu), 82.8 (1C, *C*-2), 84.9 (1C, *C*-3), 102.4 (1C, *C*-1), 117.0 (1C, *C*-7), 133.8 (1C, *C*-8), 169.0, 169.3, 169.7 (3C, *C*OO*t*Bu)

Mixture 12 (3 compounds). 80%; $Rf = 0.55$–0.70 (H:E, 4:1); ^{13}C NMR: δ 27.69 (3×6C, O*t*Bu), 63.32, 63.43, 63.54 (3×1C, *C*-5), 68.00, 68.73, 68.96 (3×1C, *C*-6), 69.03, 69.60, 69.81, 70.64, 70.70, 73.01, 73.63, 74.20, 75.10 (3×3C, *C*H_2Ph, *C*H_2COO*t*Bu), 76.40, 77.86, 78.11, 81.28, 82.55, 82.87, 83.20, 84.42, 84.97 (3×3C, *C*-2, *C*-3, *C*-4), 80.50, 80.73, 80.99, 81.06 (3×2C, O*t*Bu), 102.16, 102.30, 102.60 (3×1C, *C*-1), 116.78, 116.83 (3×1C, *C*-7), 127.20, 127.31, 127.44, 127.53, 127.63, 127.89, 127.97 (3×5C, *C*H Ph), 133.41, 133.58 (3×1C, *C*-8), 138.00, 138.08, 138.33 (3×1C, *C* Ph), 168.54, 168.76, 168.86, 168.99, 169.24, 169.38 (3×2C, *C*OO*t*Bu).

Mixture 13 (3 compounds). 96%; $Rf = 0.55$–0.70 (H:E, 4:1); ^{13}C NMR: δ 27.94 (3×3C, O*t*Bu), 63.68, 63.74, 63.90 (3×1C, *C*-5), 68.31, 69.31, 69.99, 70.06, 70.28,

71.05, 73.25, 74.69, 74.71, 75.42, 75.47 (3×4C, *C*-6, *C*H_2Ph, *C*H_2COO*t*Bu), 77.20, 77.29, 78.88, 81.42, 81.80, 83.18, 83.86, 84.95 (3×3C, *C*-2, *C*-3, *C*-4), 81.06, 81.69, 81.75 (3×1C, O*t*Bu), 102.58, 102.88, 103.07 (3×1C, *C*-1), 117.10, 117.16, 117.19 (3×1C, *C*-7), 127.49, 127.66, 127.88, 127.93, 128.02, 128.14, 128.18, 127.27 (3×10C, *C*H Ph), 133.94 (3×1C, *C*-8), 138.06, 138.16, 138.30, 138.41, 138.65 (3×2C, *C* Ph), 169.04, 169.08, 169.46 (3×1C, *C*OO*t*Bu).

Mixtures **19**–**23** were obtained by ozonolysis/reduction of libraries **14**–**18**.

Mixture 19 (7 compounds). 84%; R_f = 0.4–0.5 (H:E, 4:1); ^{13}C NMR: δ 27.56 (1×9C, 3×6C, 3×3C, O*t*Bu), 59.58, 59.77, 59.83, 59.93, 60.16 (7×1C, *C*-5), 61.37 (7×1C, *C*-7), 68.29, 68.97, 69.14, 69.25, 69.30, 69.63, 69.75, 69.84, 70.06, 70.86, 70.90, 70.97, 71.04, 72.96, 73.09, 73.22, 73.35, 73.54, 75.45 (7×4C, *C*-6, *C*H_2Ph, *C*H_2COO*t*Bu), 77.44, 77.91, 78.09, 78.24, 78.83, 78.90, 79.00, 79.21, 79.27, 79.51, 80.03, 80.36, 80.81, 80.89, 81.37, 81.39, 81.61, 82.36, 82.63, 82.76, 82.92 (7×3C, *C*-2, *C*-3, *C*-4), 81.04, 81.13, 81.48, 81.69 (1×3C, 3×2C, 3×1C, O*t*Bu), 97.35, 97.44, 97.58, 97.75, 97.92, 98.05 (7×1C, *C*-1), 127.57, 127.83, 127.95, 128.23, 128.30 (3×10C, 3×5C, *C*H Ph), 137.64, 137.81, 137.94, 138.11, 138.28, 138.40, 138.44 (3×2C, 3×1C, *C* Ph), 169.15, 169.19, 169.34, 169.41, 169.47, 169.66, 169.71, 169.80, 169.96 (1×3C, 3×2C, 3×1C, *C*OO*t*Bu).

Mixture 20 (7 compounds). 95%; R_f = 0.4–0.5 (H:E, 4:1); ^{13}C NMR: δ 28.11 (1×9C, 3×6C, 3×3C, O*t*Bu), 61.83, 62.05 (7×1C, *C*-7), 63.71, 63.82, 63.85, 63.91, 63.99, 64.07 (7×1C, *C*-5), 69.38, 69.41, 69.44, 70.42, 70.61, 70.74, 70.99, 71.07, 71.15, 72.37, 72.52, 72.57, 73.32, 73.35, 74.87, 75.01, 75.04, 75.54, 75.57 (7×4C, *C*-6, *C*-9, *C*H2Ph, *C*H_2COO*t*Bu), 77.21, 77.29, 77.61, 78.14, 78.27, 78.77, 78.89, 78.94, 79.05, 81.43, 81.55, 81.88, 83.01, 83.08, 83.52, 83.56, 83.64, 83.79, 84.03, 85.04, 85.12, 85.25, 85.36 (7×3C, *C*-2, *C*-3, *C*-4), 81.30, 81.35, 81.66, 81.75 (1×3C, 3×2C, 3×1C, O*t*Bu), 103.59, 103.76, 104.31, 104.53 (7×1C, *C*-1), 127.64, 127.73, 127.80, 127.84, 127.87, 127.91, 127.96, 128.01, 128.15, 128.32, 128.35, 128.43 (3×5C, 3×10C, *C*H Ph), 138.03, 138.09, 138.14, 138.28, 138.37, 138.40, 138.43, 138.46, 138.57 (3×1C, 3×2C, *C* Ph), 169.14, 169.33, 169.53, 169.69, 169.72, 169.83, 169.96 (1×3C, 3×2C, 3×1C, *C*OO*t*Bu).

Mixture 21 (2 compounds). 87%; R_f = 0.4–0.5 (H:E, 4:1); ^{13}C NMR: δ 28.10, 28.19, 28.66 (2×9C, O*t*Bu), 59.39, 63.46 (2×1C, *C*-5), 61.20, 61.33 (2×1C, *C*-7), 68.83, 68.97, 69.45, 69.79, 69.99, 70.62, 70.69, 71.79 (2×4C, *C*-6, *C*H_2COO*t*Bu), 77.74, 78.75, 80.16, 82.71, 84.83 (2×3C, *C*-2, *C*-3, *C*-4), 81.02, 81.38, 81.54 (2×3C, O*t*Bu), 97.46, 103.23 (2×1C, *C*-1), 169.13, 169.33, 169.49, 169.58, 169.67 (2×3C, *C*OO*t*Bu).

Mixture 22 (6 compounds). 87%; R_f = 0.4–0.5 (H:E, 4:1); ^{13}C NMR: δ 28.11 (6×6C, O*t*Bu), 59.74, 59.88, 59.99, 63.66, 63.84, 63.92 (6×1C, *C*-5), 61.25, 61.39, 61.54, 61.64 (6×1C, *C*-7), 68.46, 69.26, 69.73, 69.89, 70.02, 70.39, 70.97, 71.08, 71.89, 73.04, 73.16, 73.24, 74.58, 75.39, 75.51 (6×4C, *C*-6, *C*H_2Ph, *C*H_2COO*t*Bu), 77.14, 78.19, 78.48, 78.67, 79.05, 79.43, 79.67, 80.19, 81.01, 81.41, 81.87, 82.93, 83.38, 83.74, 84.91, 85.28 (6×3C, *C*-2, *C*-3, *C*-4), 81.47, 81.54, 81.61, 81.69, 82.83 (6×2C, O*t*Bu), 97.23, 97.94, 98.01, 103.59, 103.76, 104.26 (6×1C, *C*-1), 127.67, 127.77, 127.98, 128.09, 128.16, 128.23, 128.35, 128.44 (6×5C, *C*H Ph), 138.12, 138.40, 138.60, 138.75 (6×1C, *C* Ph), 169.26, 169.40, 169.59, 169.65, 169.86, 170.10 (6×2C, *C*OO*t*Bu).

Mixture 23 (6 compounds). 91%; R_f = 0.4–0.5 (H:E, 4:1); ^{13}C NMR: δ 28.33 (6×3C, O*t*Bu), 60.25, 60.31, 60.43, 64.05, 64.09, 64.30 (6×1C, *C*-5), 61.89, 62.05, 62.26 (6×1C, *C*-7), 69.69, 69.79, 70.35, 70.63, 70.98, 71.40, 71.51, 72.60, 72.73, 73.60, 73.71, 73.89, 74.08, 75.29, 75.84, 75.94 (6×4C, *C*-6, *C*H_2Ph, *C*H_2COO*t*Bu), 77.53, 77.87, 78.55, 79.17, 79.38, 79.44, 79.95, 81.29, 81.67, 81.81, 81.86, 82.12, 82.82, 83.79, 83.85, 84.27, 85.35 (6×3C, *C*-2, *C*-3, *C*-4), 82.04, 82.20 (6×1C, O*t*Bu), 98.00, 98.15, 98.55, 103.99, 104.55, 104.75 (6×1C, *C*-1), 127.97, 128.04, 128.07, 128.31, 128.39, 128.43, 128.67, (6×10C, *C*H Ph), 138.05, 138.26, 138.38, 138.53, 138.63, 138.65, 138.83 (6×2C, *C* Ph), 169.43, 169.61, 169.85, 169.94, 170.07, 170.26 (6×1C, *C*OO*t*Bu).

Bromination

Mixture 24 (7 compounds). 88%; R_f = 0.4–0.55 (H:E, 4:1); ^{13}C NMR: δ 27.82 (1×9C, 3×6C, 3×3C, O*t*Bu), 29.57 (7×1C, *C*-7), 59.86, 59.98, 60.08 (7×1C, *C*-5), 67.63, 67.84, 68.99, 69.10, 69.27, 69.33, 69.51, 69.63, 70.84, 70.96, 71.00, 72.95, 73.14, 73.19, 75.39 (7×4C, *C*-6, *C*H_2Ph, *C*H_2COO*t*Bu), 77.15, 77.75, 77.97, 78.67, 78.72, 79.10, 79.36, 79.47, 79.87, 80.33, 80.40, 81.20, 81.48, 82.17, 82.48, 82.64, 82.80 (7×3C, *C*-2, *C*-3, *C*-4), 80.85, 80.94, 81.14, 81.24, 81.31 (1×3C, 3×2C, 3×1C, O*t*Bu), 96.73, 96.89, 96.99, 97.51, 97.74, 97.90 (7×1C, *C*-1), 127.38, 127.50, 127.62, 127.75, 127.91, 128.15 (3×10C, 3×5C, *C*H Ph), 137.92, 138.08, 138.27, 138.40, 138.47 (3×2C, 3×1C, *C* Ph), 169.07, 169.27, 169.39, 169.42, 169.52, 169.63, 169.78 (1×3C, 3×2C, 3×1C, *C*OO*t*Bu).

Mixture 25 (7 compounds). 88%; R_f = 0.4–0.55 (H:E, 4:1); ^{13}C NMR: δ 27.45 (1×9C, 3×6C, 3×3C, O*t*Bu), 29.55, 29.61, 29.70, 29.74 (7×1C, *C*-7), 63.33, 63.39, 63.53 (7×1C, *C*-5), 68.84, 68.98, 69.02, 69.50, 69.70, 69.86, 70.46, 70.52, 70.56, 70.61, 72.80, 72.84, 72.94, 74.11, 74.26, 74.28, 75.00, 75.04, (7×4C, *C*-6, *C*H_2Ph, *C*H_2COO*t*Bu), 76.63, 76.69, 77.00, 77.58, 77.80, 78.32, 80.78, 80.88, 81.13, 82.03, 82.42, 82.57, 82.82, 83.27, 84.10, 84.34, 84.39, 84.61 (7×3C, *C*-2, *C*-3, *C*-4), 80.61, 80.67, 80.75, 80.96, 81.01, 81.10 (1×3C, 3×2C, 3×1C, O*t*Bu), 103.05, 103.20, 103.43, 103.63 (7×1C, *C*-1), 127.02, 127.09, 127.27, 127.31, 127.46, 127.56, 127.60, 127.71, 127.75, 127.83, 127.87 (3×10C, 3×5C, *C*H Ph), 137.54, 137.69, 137.81, 137.93, 138.16 (3×2C, 3×1C, *C* Ph), 168.61, 168.70, 168.84, 169.38, 169.73 (1×3C, 3×2C, 3×1C, *C*OO*t*Bu).

Mixture 26 (2 compounds). 87%; R_f = 0.4–0.55 (H:E, 4:1); ^{13}C NMR: δ 27.99 (2×9C, O*t*Bu), 29.64, 29.99 (2×1C, *C*-7), 60.02, 63.96 (2×1C, *C*-5), 67.96, 69.18, 69.39, 69.43, 69.55, 69.94, 70.90, 71.00 (2×4C, *C*-6, *C*H_2 COO*t*Bu), 77.45, 78.86, 80.02, 82.51, 82.98, 84.86 (2×3C, *C*-2, *C*-3, *C*-4), 81.05, 81.19, 81.39, 81.44, 81.48 (2×3C,

O*t*Bu), 97.69, 103.49 (2×1C, *C*-1), 169.13, 169.23, 169.32, 169.56, 169.80, 169.82 (2×3C, *C*OO*t*Bu).

Mixture 27 (6 compounds). 89%; R_f = 0.4–0.55 (H:E, 4:1); ^{13}C NMR: δ 27.90 (6×6C, O*t*Bu), 29.61, 29.91, 30.05 (6×1C, *C*-7), 59.94, 60.07, 60.18, 63.73, 63.82, 63.92 (6×1C, *C*-5), 67.67, 67.92, 68.30, 69.22, 69.36, 69.63, 70.07, 70.94, 71.05, 73.06, 73.30, 74.48, 75.35, 75.47 (6×4C, *C*-6, *C*H$_2$Ph, *C*H$_2$COO*t*Bu), 77.83, 77.95, 78.06, 78.17, 79.21, 79.41, 79.59, 80.47, 81.25, 81.57, 82.40, 82.56, 82.73, 83.19, 84.46, 84.99 (6×3C, *C*-2, *C*-3, *C*-4), 81.08, 81.45 (6×2C, O*t*Bu), 96.84, 97.85, 103.42, 103.54, 104.79 (6×1C, *C*-1), 127.45, 127.57, 127.68, 127.84, 127.92, 128.00, 128.11, 128.23 (6×5C, *C*H Ph), 138.00, 138.07, 138.18, 138.32 (6×1C, *C* Ph), 168.98, 169.11, 169.21, 169.38, 169.62, 169.75, 169.89 (6×2C, *C*OO*t*Bu).

Mixture 28 (6 compounds). 89%; R_f = 0.4–0.55 (H:E, 4:1); ^{13}C NMR: δ 27.94 (6×3C, O*t*Bu), 29.68, 30.02, 30.16 (6×1C, *C*-7), 60.12, 60.21, 60.28, 63.73, 63.84, 63.98 (6×1C, *C*-5), 67.76, 68.00, 69.27, 69.43, 69.80, 70.27, 71.03, 71.16, 73.19, 73.33, 74.68, 75.44, 75.55 (6×4C, *C*-6, *C*H$_2$Ph, *C*H$_2$COO*t*Bu), 77.10, 77.28, 78.11, 78.74, 78.87, 79.19, 79.57, 80.44, 81.21, 81.34, 81.39, 81.56, 82.32, 82.83, 83.00, 83.68, 84.76 (6×3C, *C*-2, *C*-3, *C*-4), 81.11, 81.48 (6×1C, O*t*Bu), 97.04, 97.12, 98.04, 103.62, 103.87, 104.05 (6×1C, *C*-1), 127.51, 127.66, 127.89, 128.00, 128.27, 129.68 (6×10C, *C*H Ph), 137.99, 138.25, 138.35, 138.58 (6×2C, *C* Ph), 168.99, 169.58, 169.78 (6×1C, *C*OO*t*Bu).

Libraries **30** and **31** were not accurately characterized due to extensive signal overlap. The following sub-libraries **32–36** prepared for the deconvolution process of the main library **31a** have been characterized. Their preparation involved amination–deprotection of the sub-libraries **24–28** according to the above general procedures.

Mixture 32 (7 compounds). 90%; ^{13}C NMR: δ 10.50 (7×1C, *C*H$_3$), 19.41 (7×1C, *C*H$_2$CH$_3$), 47.08 (7×1C, *C*-7), 49.55°(7×1C, *C*H$_2$N), 59.35, 59.66, 63.02°(7×2C, *C*-5, *C*-6), 68.07, 68.24, 68.41, 68.53, 68.72, 68.89, 69.21, 69.97, 73.46, 74.04, 75.67 (7×3C, *C*H$_2$COOH, *C*H$_2$Ph), 77.30, 78.02, 78.27, 78.54, 78.68, 79.36, 80.19, 80.35, 80.56, 80.78, 80.97, 81.59, 81.71°(7×3C, *C*-2, *C*-3, *C*-4), 96.77, 97.18 (7×1C, *C*-1), 116.67 (q, $J_{C,F}$ 290 Hz, *C*F$_3$), 128.95, 129.14 (3×5C, 3×10C, *C*H Ph), 137.14, 137.39, 137.58, 137.84 (3×1C, 3×2C, *C* Ph), 163.16 (q, $J_{C,F}$ 35 Hz, *C*OCF$_3$), 173.95, 174.34, 174.48, 174.66 (3×1C, 3×2C, 1×3C, *C*OOH).

Mixture 33 (7 compounds). 94%; ^{13}C NMR: δ 9.97 (7×1C, *C*H$_3$), 18.86 (7×1C, *C*H$_2$CH$_3$), 46.69 (7×1C, *C*-7), 48.77, 48.98 (7×1C, *C*H$_2$N), 62.26, 62.49, 62.84, 64.49, 64.82 (7×2C, *C*-5, *C*-6), 67.57, 69.03, 69.18, 69.42, 72.79, 72.89, 74.37, 74.87 (7×3C, *C*H$_2$COOH, *C*H$_2$Ph), 76.40, 76.75, 77.55, 77.88, 78.13, 78.27, 79.82, 80.21, 80.39, 81.41, 81.55, 81.90, 82.09, 82.73, 82.97 (7×3C, *C*-2, *C*-3, *C*-4), 101.97, 102.16, 102.36, 102.55 (7×1C, *C*-1), 116.16 (q, $J_{C,F}$ 290 Hz, *C*F$_3$), 128.28, 128.48, 128.64 (3×5C, 3×10C, *C*H Ph), 137.00, 137.27 (3×1C, 3×2C, *C* Ph), 162.62 (q, $J_{C,F}$ 35 Hz, *C*OCF$_3$), 173.82, 174.13, 174.48 (3×1C, 3×2C, 1×3C, *C*OOH).

Mixture 34 (2 compounds). 95%; ^{13}C NMR: δ 10.17 (2×1C, *C*H$_3$), 19.03, 19.09 (2×1C, *C*H$_2$CH$_3$), 46.83, 46.89 (2×1C, *C*-7), 49.23, 49.28 (2×1C, *C*H$_2$N), 58.94, 62.44, 62.69, 64.61 (2×2C, *C*-5, *C*-6), 67.88, 68.10, 68.65, 69.26, 69.65, 69.78 (2×3C, *C*H$_2$COOH), 77.71, 78.05, 80.04, 81.58, 81.72, 83.44 (2×3C, *C*-2, *C*-3, *C*-4), 96.40, 102.10 (2×1C, *C*-1), 116.90 (q, $J_{C,F}$ 290 Hz, *C*F3), 163.24 (q, $J_{C,F}$ 35 Hz, *C*OCF$_3$), 173.78, 174.14, 174.19, 174.29, 174.47 (2×3C, *C*OOH).

Mixture 35 (6 compounds). 94%; ^{13}C NMR: δ 10.80, 10.84 (6×1C, *C*H3), 19.72 (6×1C, *C*H$_2$CH$_3$), 47.51 (6×1C, *C*-7), 49.86, 49.94 (6×1C, *C*H$_2$N), 59.68, 59.89, 63.02, 63.27, 65.29 (6×2C, *C*-5, *C*-6), 68.41, 68.57, 68.90, 69.46, 69.54, 69.89, 70.10, 70.18, 70.35, 73.48, 73.71, 74.25, 74.59, 75.11, 75.65, 75.98 (6×3C, *C*H$_2$ COOH, *C*H$_2$Ph), 77.26, 77.67, 78.29, 78.47, 78.95, 79.61, 80.54, 80.70, 80.93, 81.01, 81.98, 82.23, 82.46, 83.65, 83.82 (6×3C, *C*-2, *C*-3, *C*-4), 96.92, 97.21, 97.39, 102.76, 103.17 (6×1C, *C*-1), 116.97 (q, $J_{C,F}$ 290 Hz, *C*F$_3$), 129.04, 129.14, 129.41, 129.53 (6×5C, *C*H Ph), 137.40, 138.87, 138.15 (6×1C, *C* Ph), 162.91 (q, $J_{C,F}$ 35 Hz, *C*OCF$_3$), 168.57, 168.68, 168.81, 168.90, 169.06, 169.17, 169.29, 169.43 (6×2C, *C*OOH).

Mixture 36 (6 compounds). 93%; ^{13}C NMR: δ 10.61 (6×1C, *C*H$_3$), 19.57, 19.65 (6×1C, *C*H$_2$CH$_3$), 47.14 (6×1C, *C*-7), 49.52 (6×1C, *C*H$_2$N), 60.02, 63.13, 63.17, 63.34, 63.48, 63.57, 64.99, 65.13 (6×2C, *C*-5, *C*-6), 68.45, 68.84, 69.59, 69.84, 70.04, 70.29, 73.18, 73.41, 73.53, 74.05, 74.24, 74.95, 75.51, 75.74 (6×3C, *C*H$_2$ COOH, *C*H$_2$Ph), 77.33, 77.60, 77.84, 78.15, 78.81, 79.10, 79.39, 79.92, 80.88, 81.13, 81.33, 81.81, 82.75, 83.18, 83.91 (6×3C, *C*-2, *C*-3, *C*-4), 97.18, 97.69, 103.01, 103.46, 103.63 (6×1C, *C*-1), 117.01 (q, $J_{C,F}$ 290 Hz, *C*F$_3$), 128.32, 128.40, 128.51, 128.86, 129.06 (6×10C, *C*H Ph), 137.55, 138.16, 138.28, 138.47, 138.59, 138.70 (6×2C, *C* Ph), 162.20 (q, $J_{C,F}$ 35 Hz, *C*OCF$_3$), 173.27, 173.48, 173.56, 173.64, 173.76, 174.16 (6×1C, *C*OOH).

Deconvolution process: final steps and resynthesis of the final compound 39 according to general procedures

Allyl 2,3-di-*O*-benzyl-4-*O*-(*tert*-butoxycarbonylmethyl)-α-D-xylopyranoside (41). Allyl 2,3-di-*O*-benzyl-α-D-xylopyranoside (**40**) (801 mg, 2.16 mmol) was treated with NaH (346 mg, 8.65 mmol) and *tert*-butylbromoacetate (1.28 mL) to provide **41** (1.01 g, 2.09 mmol, 97%) as a colorless oil; R_f = 0.52 (H:E, 4:1); $[\alpha]_D$ +39.5 (*c* 1.0, $CHCl_3$); IR: 1747 cm^{-1}; ^{1}H NMR: δ 1.48 (s, 9H, *t*Bu), 3.47 (m, 2H, *H*-2, *H*-5), 3.60 (dd, 1H, $J_{2,3}$ 10.5, $J_{3,4}$ 10.5 Hz, *H*-3), 3.82 (ddd, 1H, $J_{4,5}$ 4, $J_{4,5'}$ 2 Hz, *H*-4), 3.92 (dd, $J_{5,5'}$ 9.5 Hz, *H*-5′), 3.98 (ddd, 1H, $J_{6,6'}$ 13, $J_{6,7}$ 7, $J_{6,8}$ 1.5 Hz, *H*-6), 4.18 (dd, 1H, $J_{6',7}$ 5 Hz, $J_{6',8}$ 1 Hz, *H*-6′), 4.18 (s, 2H, C*H*$_2$COO*t*Bu), 4.63 (d, 1H, J_{gem} 12 Hz, C*H*$_2$Ph), 4.73 (d, 1H, $J_{1,2}$ 4 Hz, *H*-1), 4.76 (d, 1H, C*H*$_2$Ph), 4.82 (d, 1H, J_{gem} 11 Hz, C*H*$_2$Ph), 4.93 (d, 1H, C*H*$_2$Ph), 5.23 (dd, 1H, $J_{7,8}$ 10.5, $J_{8,8'}$ 1.5 Hz, *H*-8), 5.33 (dd, 1H, $J_{7,8'}$ 17 Hz, *H*-8′), 5.94 (m, 1H, *H*-7), 7.34 (m, 10H, Ph); ^{13}C NMR: δ 27.9 (3C, *t*-Bu), 60.0 (1C, *C*-5), 67.9 (1C, *C*-6), 69.4 (1C, *C*H$_2$COO*t*Bu), 73.0, 75.5 (2C, *C*H$_2$Ph), 79.0, 79.5 (2C, *C*-2, *C*-4), 81.4 (1C, *C*-3), 81.5

(1C, $C(CH_3)_3$), 95.4 (1C, *C*-1), 117.9 (1C, *C*-8), 127.45, 127.66, 127.85, 127.93, 128.20, 128.24 (10C, *C*H Ph), 133.6 (1C, *C*-7), 138.0, 138.6 (2C, *C* Ph), 169.6 (1C, *C*OO*t*Bu); EIMS (*m*/*z*): 485.0 $(M+H)^{+\bullet}$, 426.9, 371.2, 277.2, 187.1, 91.1.

(2-Hydroxy-ethyl) 2,3-di-*O*-benzyl-4-*O*-(*tert*-butoxycarbonylmethyl)-α-D-xylopyranoside (42). Compound **41** (1.00 g, 2.07 mmol) was treated with O_3 then sodium borohydride (312 mg, 8.2 mmol) to yield **42** (995 mg, 2.04 mmol, 98%) as a colorless oil; R_f = 0.50 (H:E, 1:4); $[\alpha]_D$ +41.8 (*c* 1.0, $CHCl_3$); IR: 3470, 1747 cm^{-1}; ^1H NMR: δ 1.47 (s, 9H, *t*Bu), 2.71 (m, 1H, O*H*), 3.47 (m, 2H, *H*-2, *H*-5), 3.53 (m, 1H, *H*-6), 3.62 (m, 1H, *H*-6′), 3.72 (m, 3H, *H*-7, *H*-7′), 3.83 (dd, $J_{4,5}$ 5, $J_{5,5'}$ 10.5 Hz, *H*-5′), 3.92 (dd, 1H, $J_{2,3}$ 10, $J_{3,4}$ 10 Hz, *H*-3), 4.18 (s, 2H, CH_2COO*t*Bu), 4.65 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.73 (d, 1H, $J_{1,2}$ 4 Hz, *H*-1), 4.75 (d, 1H, CH_2Ph), 4.83 (d, 1H, J_{gem} 11 Hz, CH_2Ph), 4.90 (d, 1H, CH_2Ph), 7.34 (m, 10H, Ph); ^{13}C NMR: δ 28.2 (3C, *t*Bu), 60.2 (1C, *C*-5), 61.6 (1C, *C*-7), 68.7 (1C, *C*-6), 69.6 (1C, *C*H_2COO*t*Bu), 73.5, 75.7 (2C, *C*H_2Ph), 79.3, 79.9 (2C, *C*-2, *C*-4), 81.7 (1C, *C*-3), 81.7 (1C, *t*Bu), 97.6 (1C, *C*-1), 127.80, 127.95, 128.17, 128.27, 128.54, 128.65 (10C, *C*H Ph), 138.1, 138.9 (2C, *C* Ph), 169.9 (1C, *C*OOtBu); EIMS (*m*/*z*): 489.3 $(M+H)^{+\bullet}$, 370.9, 277.2, 187.1, 91.1. Anal. calcd for $C_{27}H_{36}O_8$: C, 66.4; H, 7.4. Found: C, 66.62; H, 7.51.

(2-Bromo-ethyl) 2,3-di-*O*-benzyl-4-*O*-(*tert*-butoxycarbonylmethyl)-α-D-xylopyranoside (43). Compound **42** (550 mg, 1.13 mmol) in DMF (40 mL) was treated with NBS (599 mg, 3.39 mmol) and PPh_3 (889 mg, 3.39 mmol) to give, after column chromatography, **43** (570 mg, 1.04 mmol, 92%) as a colorless oil; R_f = 0.55 (H:E, 4:1); $[\alpha]_D$ +61.3 (*c* 1.1, $CHCl_3$); IR: 1746 cm^{-1}; ^1H NMR: δ 1.46 (s, 9H, *t*-Bu), 3.45 (2dd, 2H, $J_{1,2}$ 4, $J_{2,3}$ 10, $J_{4,5}$ 4, $J_{5,5'}$ 10 Hz, *H*-2, *H*-5), 3.52 (t, 2H, $J_{6,7}$ 6.5 Hz, *H*-7, *H*-7′), 3.65 (dd, 1H, $J_{4,5'}$ 10 Hz, *H*-5′), 3.80 (m, 1H, *H*-4), 3.88 (m, 3H, *H*-3, *H*-6, *H*-6′), 4.19 (s, 2H, CH_2COO*t*Bu), 4.66 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.71 (d, 1H, *H*-1), 4.78 (d, 1H, CH_2Ph), 4.83 (d, 1H, J_{gem} 11 Hz, CH_2Ph), 4.93 (d, 1H, CH_2Ph), 7.34 (m, 10H, Ph); ^{13}C NMR: δ 28.4 (3C, *t*Bu), 30.2 (1C, *C*-7), 60.7 (1C, *C*-5), 68.2 (1C, *C*-6), 69.8 (1C, *C*H_2COO*t*Bu), 73.5, 75.8 (2C, *C*H_2Ph), 79.3, 80.0 (2C, *C*-2, *C*-4), 81.76 (1C, *C*-3), 81.84 (1C, *C*$(CH_3)_3$), 97.4 (1C, *C*-1), 127.92, 128.19, 128.33, 128.65, 128.72 (10C, *C*H Ph), 137.4, 138.0 (2C, *C* Ph), 170.0 (1C, *C*OO*t*Bu); EIMS (*m*/*z*): 553.4 $(M+2+H)^{+\bullet}$, 551.3 $(M+H)^{+\bullet}$, 459.1, 461.2, 369.2, 370.9, 263.1, 187.1, 91.1. Anal. calcd for $C_{27}H_{35}O_7Br$: C, 58.8; H, 6.4. Found C, 58.74; H, 6.26.

(2-Propylamino-ethyl) 2,3-di-*O*-benzyl-4-*O*-(*tert*-butoxycarbonylmethyl)-α-D-xylopyranoside (44). Compound **43** (351 mg, 0.64 mmol) in DMF (30 mL) was reacted with propylamine (3 mL) to afford **44** (331 mg, 0.63 mmol, 98%) as a colorless oil; R_f = 0.55 (CH_2Cl_2:MeOH, 9:1); $[\alpha]_D$ +58.8 (*c* 1.0, $CHCl_3$); IR: 3306, 1747 cm^{-1}; ^1H NMR: δ 0.89 (t, 3H, *J* 7.5 Hz, CH_3), 1.46 (s, 9H, *t*-Bu), 1.52 (m, 2H, CH_2CH$_3$), 1.90 (m, 1H, N*H*), 2.57 (t, 2H, *J* 7.5 Hz, CH_2NH), 2.82 (m, 2H, *H*-7, *H*-7′), 3.42 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 10 Hz, *H*-2), 3.52 (m, 3H, *H*-4, *H*-5, *H*-6), 3.80 (m, 3H, *H*-3, *H*-5′, *H*-6′), 4.17 (s, 2H, CH_2 COO*t*Bu), 4.62 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.71 (d, 1H, *H*-1), 4.73 (d, 1H, CH_2Ph), 4.81 (d, 1H, J_{gem} 11 Hz, CH_2Ph), 4.91 (d, 1H, CH_2Ph), 7.34 (m, 10H, Ph); ^{13}C NMR: δ 11.1 (1C, *C*H3), 22.4 (1C, *C*H2), 27.9 (3C, *t*-Bu), 47.5 (1C, *C*-7), 49.7 (1C, *C*H2N), 60.0 (1C, *C*-5), 63.0 (1C, *C*-6), 69.4 (1C, *C*H_2COO*t*Bu), 74.0, 75.6 (2C, *C*H_2Ph), 78.9, 79.5 (2C, *C*-2, *C*-4), 81.0 (1C, *C*-3), 82.1 (1C, *t*-Bu), 96.9 (1C, *C*-1), 127.82, 127.94, 128.43, 128.59, 128.65 (10C, *C*H Ph), 137.0, 138.3 (2C, *C* Ph), 169.9 (1C, *C*OO*t*Bu); EIMS (*m*/*z*): 530.1 $(M+H)^{+\bullet}$, 500.6, 474.6, 467.8, 439.8, 427.8, 397.9, 114.1, 91.0.

(*N*-(*tert*-Butoxycarbonyl)-2-propylamino-ethyl) 2,3-di-*O*-benzyl-4-*O*-(*tert*-butoxy carbonylmethyl)-α-D-xylopyranoside (45). Compound **44** (321 mg, 0.61 mmol) was treated with BOC_2O (0.095 mL, 1 mmol) and triethylamine (0.155 mL, 1 mmol) to give **45** (345 mg, 0.55 mmol, 90%); R_f = 0.50 (H:E, 4:1); $[\alpha]_D$ +50.5 (*c* 1.8, $CHCl_3$); IR: 1748, 1694 cm^{-1}; ^1H NMR: δ 0.85 (t, 3H, *J* 7.5 Hz, CH_3), 1.44 (s, 18H, *t*-Bu), 1.53 (m, 2H, CH_2CH$_3$), 3.21 (t, 2H, *J* 7.5 Hz, *C*H$_2$N), 3.42 (m, 6H, *H*-2, *H*-4, *H*-5, *H*-6, *H*-7, *H*-7′), 3.81 (m, 3H, *H*-3, *H*-5′, *H*-6′), 4.18 (s, 2H, CH_2COO*t*Bu), 4.62 (d, 1H, J_{gem} 12 Hz, CH_2Ph), 4.71 (m, 2H, *H*-1, CH_2Ph), 4.81 (d, 1H, J_{gem} 11 Hz, CH_2Ph), 4.91 (d, 1H, CH_2Ph), 7.33 (m, 10H, Ph); ^{13}C NMR: δ 11.5 (1C, *C*H$_3$), 21.7, 22.1 (1C, *C*H$_2$), 28.3, 28.7 (6C, *t*Bu), 47.0 (1C, *C*-7), 50.0, 50.5 (1C, *C*H$_2$NH), 60.3 (1C, *C*-5), 66.6 (m, 1C, *C*-6), 69.7 (1C, *C*H$_2$ COO*t*Bu), 73.4 (1C, *C*H$_2$Ph), 75.8 (1C, *C*H$_2$Ph), 79.2, 80.0 (2C, *C*-2, *C*-4), 79.5, 81.7 (2C, *t*Bu), 81.7 (1C, *C*-3), 97.3, 97.4 (1C, *C*-1), 127.84, 128.05, 128.31, 128.57 (10C, *C*H Ph), 138.5, 139.0 (2C, *C* Ph), 155.65 (d, 1C, *C*OO*t*Bu), 169.9 (1C, *C*OO*t*Bu); EIMS (*m*/*z*): 630.7 $(M+H)^{+\bullet}$, 575.1, 530.5, 474.7, 439.7, 276.9, 186.2, 130.0, 91.1. Anal. calcd for $C_{35}H_{51}NO_9$: C, 66.7; H, 8.2; N, 2.2. Found: C, 66.61; H, 8.20; N, 2.07.

(*N*-2-Propyl-aminoethyl) 2,3-di-*O*-benzyl-4-*O*-(carboxymethyl)-α-D-xylopyranoside (39). Compound **45** (321 mg, 0.51 mmol) was treated with aqueous trifluoroacetic acid (TFA:H_2O, 3:1, 10 mL) to provide, after lyophilization, trifluoroacetate salt **39** (289 mg, 0.51 mmol, 99%) as an amorphous solid; $[\alpha]_D$ +56.8 (*c* 0.8, CH_3OH); ^1H NMR (CD_3OD): δ 0.96 (t, 3H, *J* 7.5 Hz, CH_3), 1.68 (m, 2H, CH_2CH$_3$), 2.98 (t, 2H, *J* 7.5 Hz, CH_2NH), 3.29 (m, 2H, *H*-7, *H*-7′), 3.53 (m, 3H, *H*-2, *H*-4, *H*-5), 3.65 (ddd, 1H, $J_{6,6'}$ 11.5, $J_{6,7}$ 5.5, $J_{6,7'}$ 5.5 Hz, *H*-6), 3.85 (m, 2H, *H*-3, *H*-5′), 3.98 (ddd, 1H, $J_{6',7}$ 5.5, $J_{6',7'}$ 5.5 Hz, *H*-6′), 4.25 (s, 2H, CH_2COOH), 4.66 (s, 2H, CH_2Ph), 4.81 (s, 2H, CH_2Ph), 4.91 (d, 1H, $J_{1,2}$ 3.5 Hz, *H*-1), 7.33 (m, 10H, Ph); ^{13}C NMR (CD_3OD): δ 10.6 (1C, *C*H$_3$), 19.5 (1C, *C*H$_2$), 47.3 (1C, *C*-7), 49.5 (1C, *C*H$_2$NH), 60.1 (1C, *C*-5), 63.0 (m, 1C, *C*-6), 68.8 (1C, *C*H$_2$COOH), 74.1, 75.8 (2C, *C*H$_2$Ph), 79.1, 80.0 (2C, *C*-2, *C*-4), 81.2 (1C, *C*-3), 97.2 (1C, *C*-1), 116.8 (q, $J_{C,F}$ 290 Hz, *C*F$_3$), 128.37, 128.52, 128.89, 128.98, 129.08 (10C, *C*H Ph), 137.6, 138.7 (2C, *C* Ph), 161.9 (q, $J_{C,F}$ 35 Hz, *C*OCF$_3$) 173.8 (1C, *C*OOH); EIMS (*m*/*z*): 474.2 $(M+H)^{+\bullet}$, 443.8, 398.7, 381.7, 291.8, 180.7, 91.0.

Cell–matrix adhesion assay

Assays of cell adhesion to matrix-coated substrata were performed on bacteriological Petri dishes. 100 μL droplets

of a 10 μg/mL solution of either fibronectin or vitronectin in phosphate-buffered saline (PBS) were deposited on bacteriological dishes and incubated overnight at 4 °C. After several rinses, the substrata were incubated 30 min with 3 mg/mL bovine serum albumin (BSA) in PBS (previously heat-inactivated for 3°min at 80 °C). The substrata were thoroughly washed and maintained in PBS until use. S180 cells were harvested with cell dissociation enzyme-free buffer (Life Technologies) for 10 min at 37 °C. Cells were pelleted by centrifugation and incubated for 45 min in DMEM containing 10% (v/v) FN-depleted FCS. Cells were then centrifuged and resuspended in DMEM. For adhesion assays, 2.5×10^3 cells were deposited on the precoated substrata in DMEM containing or not the peptidomimetic competitors or RGDS peptide. The dishes were incubated at 37 °C for 1 h, rinsed with PBS to remove the non-adherent cells, and fixed in 5% glutaraldehyde in PBS. Cells were observed and images were recorded using a Nikon phase contrast microscope equipped with a high performance CCD camera. The images were transferred to a Power Macintosh G3 computer. Cell adhesion was then quantified by colorimetric analysis. Briefly, cells were stained with 1% crystal violet in 200 mM 2*N*-morpholino ethane sulfonic acid (MES) and rinsed in 200 mM MES buffer, pH 6. The crystal violet fixed to the cells was dissolved in 10% acetic acid and optical density (O.D.) was measured at 570 nm. The control values correspond to the O.D. obtained for cells deposited on BSA. 100% cell adhesion corresponds to the value obtained on FN-coated substratum at 50 μg/mL. The extent of cell spreading was quantified using Scion Image software by measuring the area of adherent cells (at least 30 cells were measured). At least three independent experiments were done for each type of substratum (fibronectin or vitronectin) and with or without competitors.

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References and Notes

1. (a) Lowe, G. *Chem. Soc. Rev.* **1995**, *24*, 309. (b) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132. (c) Cortese, R., Ed.; Walter de Gruyter: Berlin, Germany, 1996.
2. Albelda, S. M.; Buck, C. A. *FASEB J.* **1990**, *4*, 2868.
3. (a) Ruoslahti, E., Pierschbacher, M. D. *Cell* **1986**, *44*, 517. (b) D'Souza, S. E.; Ginsberg, M.H.; Burke, T. A.; Lam, S. C. T.; Plow, E. F. *Science* **1988**, *242*, 91.
4. (a) Ruoslahti, E.; Pierschbacher, M. D. *Science* **1987**, *238*, 491. (b) Gurrath, M.; Müller, G.; Kessler, H.; Aumailley, M.; Timpl, R. *Eur. J. Biochem.* **1992**, *210*, 911. (c) Suvire, F.; Floridia, R.; Giannini, F.; Rodriguez, A.; Enriz, R.; Jauregui, E. *Molecules* **2000**, *5*, 583.
5. (a) Nichols, A. J.; Ruffolo, R.R.; Huffman, W.F.; Poste, G., Samanen, J. *TiPS* **1992**, *13*, 413. (b) Samanen, J. *Annu. Rep. Med. Chem.* **1996**, *31*, 91.
6. (a) Samanen, J. M.; Ali, F. E.; Barton, L. S.; Bondinell, W. E.; Burgess, J. L.; Callahan, J. F.; Calvo, R. R.; Chen, W.; Chen, L.; Erhard, K.; Feuerstein, G.; Heys, R.; Hwang, S. M.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Kwon, C.; Lee, C. P.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M.; Peishoff, C. E.; Rhodes, G.; Ross, S, Shu, A.; Simpson, R.; Takata, D.; Yellin, T. O.; Uzsinskas, I.; Venslavsky, J. W.; Yuan, C.-K.; Huffman, W. F. *J. Med. Chem.* **1996**, *39*, 4867. (b) Corbett, J. W.; Graciani, N. R.; Mousa, S. A.; DeGrado, W. F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1371. (c) Nicolaou, K. C.; Trujillo, J. I.; Jandeleit, B.; Chibale, K.; Rosenfeld, M.; Diefenbach, B.; Cheresh, D. A.; Goodman, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1185. (d) Keenan, R. M.; Callahan, J. F.; Samanen, J. M.; Bondinell, W. E.; Calvo, R. R.; Chen, L.; DeBrosse, C.; Eggleston, D. S.; Haltiwanger, R. C.; Hwang, S. M.; Jakas, D. R.; Ku, T. W.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M. F.; Southhall, L. S.; Uzinskas, I.; Vasko-Moser, J. A.; Venslavsky, J. W.; Wong, A. S.; Huffman, W. F. *J. Med. Chem* **1999**, *42*, 545. (e) Miller, W. H.; Alberts, D. P.; Bhatnagar, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P. J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J. W.; Yuan, C. C.; Haltiwanger, R. C.; Gowen, M.; Hwang, S. M.; James, I. E.; Lark, M. W.; Rieman, D. J.; Stroup, G. B. *J. Med. Chem.* **2000**, *43*, 22. (f) Pitts, W. J.; Wityak, J.; Smallheer, J. M.; Tobin, A. E.; Jetter, J. W.; Buynitsky, J. S.; Harlow, P. P.; Solomon, K. A.; Corjay, M. H.; Mousa, S. A.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 27. (g) Peyman, A.; Wehner, V.; Knolle, J.; Stilz, H. U.; Breipohl, G.; Scheunemann, K.-H.; Carniato, D.; Ruxer, J.-M.; Gourvest, J.-F.; Gadek, T. R.; Bodary, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 179. (h) Osterkamp, F.; Ziemer, B.; Koert, U.; Wiesner, M.; Raddatz, P., Goodman, S. L. *Chem. Eur. J.* **2000**, *6*, 666.
7. (a) Bach, A. C. II; Espina, J. R.; Jackson, S. A.; Stouten, P. F. W.; Duke, J. L.; Mousa, S. A.; DeGrado, W. F. *J. Am. Chem. Soc.* **1996**, *118*, 293. (b) Peishoff, C. E.; Ali, F. E.; Bean, J. W.; Calvo, R.; D'Ambrosio, C. A.; Eggleston, D. S.; Hwang, S. M.; Kline, T. P.; Koster, P. F.; Nichols, A.; Powers, D.; Romoff, T.; Samanen, J. M.; Stadel, J.; Vasko, J. A.; Kopple, K. D. *J. Med. Chem.* **1992**, *35*, 3962. (c) Burgess, K.; Lim, D. *J. Med. Chem.* **1996**, *39*, 4520. (d) Tran, T.-A.; Mattern, R.-H.; Zhu, Q.; Goodman, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 997. (e) Nikiforovich, G. V.; Kover, K. E.; Zhang, W. J.; Marshall, G. R. *J. Am. Chem. Soc.* **2000**, *122*, 3262.
8. (a) Haubner, R.; Gratias, R.; Diefenbach, B.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7461. (b) Haubner, R.; Schmitt, W.; Holzemann, G.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7881. (c) Wermuth, J., Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1997**, *119*, 1328. (d) Haubner, R.; Finsinger, D.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1375; *Angew. Chem.* **1997**, *109*, 1440.
9. (a) Minoux, H.; Moitessier, N.; Chapleur, Y.; Maigret, B. *Lett. Pept. Sci.* **1997**, *4*, 463. (b) Minoux, H.; Moitessier, N.; Chapleur, Y.; Maigret, B. *J. Comput. Aid. Mol. Design* **1998**, *12*, 533. For calculations on RGD containing cyclic peptides see refs 17 and 7e.
10. Moitessier, N.; Minoux, H.; Maigret, B.; Chrétien, F.; Chapleur, Y. *Lett. Pept. Sci.* **1998**, *5*, 75.
11. (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B. III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (b) Papageorgiou, C.; Haltiner, R.; Bruns, C.; Petcher, T. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 135. (c) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shake-

speare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B. III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. A.; Strader, C. D. *J. Am. Chem. Soc*. **1993**, *115*, 12550. (d) LeDiguarher, T.; Boudon, A.; Elwell, C.; Paterson, D. E.; Billington, D. C. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1983. (e) Smith, A. B. III; Sasho, S.; Barwis, B. A.; Sprengeler, P.; Barbosa, J.; Hirschmann, R.; Cooperman, B. S. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3133. (f) Gauzy, L.; Le Merrer, Y.; Depezay, J. C.; Clerc, F.; Mignani, S. *Tetrahedron Lett*. **1999**, *40*, 6005. (g) Hanessian, S.; Saavedra, O.; Xie, F.; Amboldi, N.; Battistini, C. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 439. (h) Xuereb, H.; Maletic, M.; Gildersleeve, J.; Pelczer, I.; Kahne, D. *J. Am. Chem. Soc*. **2000**, *122*, 1883.

12. (a) Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C. H. *J. Am. Chem. Soc*. **1996**, *118*, 10150. (b) Kanie, O.; Barresi, F.; Ding, Y. L.; Labbe, J.; Otter, A.; Forsberg, L. S.; Ernst, B.; Hindsgaul, O. *Angew. Chem. Int. Ed. Engl*. **1996**, *34*, 2720. (c) Kallus, C.; Opatz, T.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Tetrahedron Lett*. **1999**, *40*, 7783. (d) Lubineau, A.; Bonnaffe, D. *Eur. J. Org. Chem*. **1999**, 2523. (e) Takahashi, T.; Adachi, M.; Matsuda, A.; Doi, T. *Tetrahedron Lett*. **2000**, *41*, 2599.

13. For reviews on sugars involving combinatorial chemistry see: (a) Sofia, M. J. *Mol. Divers*. **1998**, *3*, 75. (b) Schweizer, F.; Hindsgaul, O. *Curr. Opin. Chem. Biol*. **1999**, *3*, 291.

14. For the use of carbohydrate scaffolds see: (a) Poitout, L.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett*. **1995**, *36*, 6887. (b) von Roedern, E. G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc*. **1996**, *118*, 10156. (c) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 2503; *Angew. Chem*. **1998**, *110*, 2620. (d) Sofia, M. J.; Hunter, R.; Chan, T. Y.; Vaughan, A.; Dulina, R.; Wang, H. M.; Gange, D. *J. Org. Chem*. **1998**, *63*, 2802. (e) Brill, W. K. D.; De Mesmaeker, A.; Wendeborn, S. *Synlett* **1998**, 1085. (f) Overkleeft, H. S.; Verhelst, S. H. L.; Pieterman, E.; Meeuwenoord, W. J.; Overhand, M.; Cohen, L. H.; vanderMarel, G. A.; vanBoom, J. H. *Tetrahedron Lett*. **1999**, *40*, 4103. See also ref. 12c.

15. (a) Gould, R. J.; Chang, C. T. C.; Lynch, R. J.; Manno, P. D.; Zhang, G.; Bednar, B.; Friedman, P. A.; Egbertson, M.; Turchi, L. M.; Anderson, P. S.; Hartman, G. *Thromb. Haemostas*. **1993**, *69*, 976. (b) Hartman, G. D.; Egbertson, M. S.; Halczenko, W.; Laswell, W. L.; Duggan, M. E.; Smith, R. L.; Naylor, A. M.; Manno, P. D.; Lynch, R. J.; Zhang, G.; Chang, C. T. C.; Gould, R. J. *J. Med. Chem*. **1992**, *35*, 4640. (c) Hartman, G. D.; Duggan, M. E.; Ihle, N. C. WO-A 95/32710-A1.

16. Keenan, R. M.; Miller, W. H.; Kwon, C.; Ali, F. E.; Callahan, J. F.; Calvo, R. R.; Hwang, S. M.; Kopple, K. D.; Peishoff, C. E.; Samanen, J. M.; Wong, A. S.; Yuan, C. K.; Huffman, W. F. *J. Med. Chem*. **1997**, *40*, 2289.

17. Dechantsreiter, M. A.; Planker, E.; Mathä, B.; Lohof, E.; Hölzemann, G.; Jonczyk, A.; Goodman, S.; Kessler, H. *J. Med. Chem*. **1999**, *42*, 3033. See also ref. 7e.

18. Moitessier, N.; Chrétien, F.; Chapleur, Y. *Tetrahedron: Asymmetry* **1997**, *6*, 2889.

19. For the sake of simplicity the coined term ''library'' was also used for **10** and **11**, which actually consisted of a single compound.

20. (a) Deprez, B.; Williard, X.; Bourel, L.; Coste, H.; Hyafil, F.; Tartar, A. *J. Am. Chem. Soc*. **1995**, *117*, 5405. (b) Pirrung, M. C.; Chen, J. *J. Am. Chem. Soc*. **1995**, *117*, 1240.

21. Erb, E.; Janda, K. D.; Brenner, S. *Proc. Natl. Acad. Sci*. **1994**, *91*, 11422.